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ORGANIC CHEMISTRY
IN PHARMACY

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ORGANIC CHEMISTRY IN PHARMACY

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Preface

In this textbook, it is our purpose to describe, within certain chemical classifications, those substances used as pharmaceutical aids and as therapeutic agents. For several years there has been a need for a textbook which would present the necessary information on organic pharmaceuticals at the undergraduate level. This volume is written for the undergraduate pharmacy student who has previously completed a regular year's course in the fundamentals of organic chemistry. The information assembled is that which is thought to be of practical value to present-day pharmacists, since it is now quite generally understood that a pharmacist should have a thorough knowledge of what a drug is, its limitations, applications, forms, and uses, as well as of those characteristics which pertain strictly to its compounding.

Products used in medicine and in pharmacy have been divided, in the main, on the basis of their chemical constitution. However, in order to have the less difficult subject matter appear first, the order of presentation is aliphatic-type compounds, followed by the aromatic, heterocyclic, and other cyclic types. As each class of organic compounds is introduced, there is a discussion of the basic principles of organic chemistry, which serves to orient the student and provide a review. Since certain terms are used in pharmacy to identify groups of pharmaceuticals, there are chapters such as Sulfur Compounds, Compounds Containing Heavy Metals, Dyes, Surface-Active Agents, Alkaloids, Antibiotics, and Vitamins.

To bring about a better understanding of why certain organic compounds have been selected as pharmaceuticals, and to impress on the student the importance of physical properties, a chapter was written on "Physical

Properties in Relation to Biologic Action." Usually, the chemical properties of a compound are responsible for the method of detoxication in the body. It is desirable for the pharmacist to be aware of the mechanisms used by the body for disposing of pharmaceuticals, as this leads to increased understanding of the applications of drugs.

A chemical classification has been used in this textbook for two principal reasons. First of all, a course in pharmaceutical chemistry is most often offered in the junior year, following the course in organic chemistry and preceding a course in pharmacology. A pharmacology outline seemed illogical inasmuch as the students are unfamiliar with this field. Secondly, by studying the chemistry and properties of a group of chemically related pharmaceuticals, it should be easier for a student, in later years, to evaluate a newly introduced pharmaceutical product. The total number of products used in medicine is enormous, and a pharmacist should understand their chemistry and not concentrate on each individually.

The authors of this book have attempted to include a discussion of all products described in the U.S.P. XIII, N.F. VIII, and New and Nonofficial Remedies, as well as the most important pharmaceuticals reported in the periodical literature. Due to the fact that an organic structure may contain two or more characteristic chemical groups, several pharmaceuticals offer more than one possibility for classification. An attempt has been made to describe them in the most logical division.

Lists of references and of selected topics are included at the end of each chapter.

CHARLES O. WILSON
OLE GISVOLD

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1

Introduction

The turn of the century has seen the development of most of the organic medicinal agents, a great majority of which have been produced in the past twenty years.

Pure organic compounds, natural or synthetic, together with the so-called organo-metallics for the cure, mitigation or prevention of disease are the chief source of agents today. These remedial agents have had their origin in essentially three ways: (1) from naturally occurring materials of both plant and animal origin, (2) from the synthesis of organic compounds whose structures are closely related to those of naturally occurring compounds that have been shown to possess useful medicinal properties, and (3) from efforts of pure synthesis in which no attempt has been made to pattern after a known, naturally occurring compound exhibiting some activity. Many of the compounds from the first group are prepared synthetically today as a financially expedient measure. Examples of these are most of the vitamins, some sex hormones, corticomimetic principles, camphor, menthol, etc. On the other hand, cardiac glycosides,

quinine, atropine, penicillin, streptomycin, vitamin A, estrone, epinephrine, either cannot be synthesized or can be isolated from natural sources at a cost that can compete with synthetic methods. Examples of compounds found in the second group are the large numbers of sympathomimetic drugs and local anesthetics, antispasmodics, mydriatic, myotic drugs, etc. Examples of the third group include the synthetic estrogens, stilbestrol and related compounds, synthetic antimalarials, dyes, most antihistaminases, some analgesics, sulfonamides, mercurials, arsenicals, phenols, barbiturates, surface active agents, etc.

Even though the isolation and synthesis of many active constituents from animal and plant sources have been accomplished, there are new problems yet to be solved. Some of these are the isolation, proof of structure and synthesis of the active constituent of the amorphous fraction of adrenal cortex extracts; proof of structure and synthesis of a highly active antimalarial alkaloid from *Dichroa febrifuga*; proof of structure and synthesis of vitamin B₁₂, the very active,

2 Introduction

antipernicious anemia factor found in liver. These accomplishments, together with others, will add to the present large number of useful organic medicinal compounds and bring about a more complete complement of drugs.

In many cases, at present, there is no simple and direct correlation between the activity of organic compounds and their chemical structure beyond the broad generalization that compounds similarly constituted may be expected to have similar activities. This is not always true, for often a fine shade of difference in chemical structure may lie between a very active compound on the one hand and a completely inactive one on the other. In other cases, each member of a whole series of compounds more or less related in structure to one another may have some activity. This can well be illustrated by sympathomimetic drugs, which include a series of compounds from the simple 2-amino heptane to epinephrine. The fact that one series of compounds, structurally related to one another, exhibits a similarity in activity, does not preclude the possibility that some other compounds, unrelated structurally, cannot have similar activity. For example, anesthetic properties are present not only in the cocaine or procaine type of molecule, but also are found in benzyl alcohol, quinine, nupercaine, phenacaine, plasmochin, etc. Nevertheless, a convenient method to study of organic chemotherapeutic agents according to a chemical classifica-

tion is, in part, a desirable method of approach, because it allows the practitioner to familiarize himself with the chemical and physical properties of such groups. This knowledge is quite important and necessary for the successful practitioner.

Sometimes the activity of a drug is chiefly dependent upon its physical and chemical properties, whereas in other instances the arrangement, position and size of the groups in a given molecule are also important and lead to a high degree of specificity. In the latter case, this high degree of specificity is usually associated with the mode of action of the drug, involving enzymes or enzyme systems.

As our knowledge of enzyme systems increases, so shall the development of more perfect organic drugs be made possible. Furthermore, this increased knowledge will help us to explain the mode of action of a number of valuable organic drugs now in use.

In order to more fully appreciate and understand organic medicinal products, the student should be well grounded in such fields as organic, physical, biologic and physiologic chemistry, bacteriology, physiology, and zoology.

It is not possible in a textbook of reasonable size to include a complete discussion of all subjects mentioned. The material presented here should provide a basis for a more detailed study of the scientific literature. It is hoped that the student will make use of some of the references for this purpose.

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2

Physical Properties in Relation to Biologic Action

GENERAL CONSIDERATIONS

SOLUBILITY AND PARTITION COEFFICIENTS

THE EFFECT OF THE HYDROGEN ION CONCENTRATION ON THE BIOLOGIC ACTIVITY OF ACIDS AND BASES

SURFACE ACTIVITY: ADSORPTION AND ORIENTATION AT SURFACES

OXIDATION-REDUCTION POTENTIALS AND BIOLOGIC ACTION

HYDROGEN BONDING AND BIOLOGIC ACTION

CHELATION AND BIOLOGIC ACTION

STERIC RELATIONSHIPS AND DRUG ACTION

RESONANCE AND BIOLOGIC ACTION

GENERAL CONSIDERATIONS

In the early development of synthetic medicinals a great deal of emphasis was given to the possible relationships existing between chemical constitution and biologic action. This investigation was stimulated by the observation of Crum-Brown and Fraser¹ that tertiary amines, having diverse pharmacologic properties when quaternized with alkyl halides, tended to give compounds showing a similar pharmacologic response.

With the development of the subject of pharmacology it became apparent that many compounds unrelated chemically may show the same general pharmacologic properties. As examples may be mentioned the

relatively large number of different chemical classes of compounds that have local anesthetic properties or that may serve as hypnotics or as analgesics. Schulemann² has pointed to the difficulty of finding "any connection between chemical compounds so differently constituted but having a similar biological action."

One of the early general attempts to correlate the action of drugs with their physical or physicochemical properties was made by Arrhenius,³ although prior to Arrhenius noteworthy contributions had been made, especially on the relationship of certain physical properties to hypnotic action.^{4,5,6,7,8} In general, the attempts to correlate physical

4 Physical Properties in Relation to Biologic Action

or physicochemical properties with biologic action have been handicapped by the fact that reactions occurring in the complex living body are not easily comparable to the much simpler systems used in the laboratory. However, many excellent correlations have been reported.

The physical and chemical properties of a molecule are determined by the number, kind and arrangement of the atoms within the molecule. Of course, it is not possible to make clear, precise distinctions between the purely physical and the purely chemical properties of compounds. However, the physical properties shown by a molecule may well determine the extent to which it can be absorbed and concentrated at the site of action and therefore can be expected to have a significant relation to the observed biologic action. The possible importance of such properties as solubility, partition coefficients, adsorption, surface activity, degree of dissociation at the pH of the body fluids, dissociation constants, interatomic distances between functional groups, redox-potentials (reduction-oxidation), resonance, hydrogen bonding, dimensional factors, chelation and the spatial configuration of the molecule are worthy of consideration. Moreover, the physical or physicochemical properties of the cells on which the drug acts are of considerable theoretic importance and interest. The physical properties of drugs can be varied through chemical modification more or less at will, but for the most part the properties of the normal cell remain constant. Living matter in a very general sense consists of an organized, highly complex colloidal system in which the cell or body fluids function as the continuous phase, and organized proteins, emulsified fats, etc., are dispersed phases. The living cell surfaces* are immersed in extracellular fluids, and those compounds reaching the cell surface must do so by means of transport through the extracellular fluids. Compounds insoluble in the

extracellular fluids and not solubilized by enzyme or other chemical action cannot be transported effectively by these fluids to the cell surface and normally can be expected to show no significant activity. If this is true, all biologically active substances must have or acquire through chemical modification some minimum solubility in the polar extracellular fluids.

It should be kept in mind, of course, that reactions involving a chemical equilibrium are influenced by the concentration of reactants and are subject to treatment by the law of mass action.

The theory that substances chemically related (cf. sulfonamides) may interfere with the normal function of the cell by competing with essential metabolites has been developed quantitatively by Gaddum.¹⁰ He has shown that the quantitative data for competitive antagonism may be treated by a simple equation. If C_1 is the concentration of the essential metabolite and C_2 the concentration of drug antagonist competing for the same receptors on or within the cell, and a and b the corresponding proportions of the receptors occupied by each so that $(1-a-b)$ is the proportion of the receptors free. Then for equilibrium:

$$K_1 C_1 (1 - a - b) = a, \text{ and} \\ K_2 C_2 (1 - a - b) = b$$

Elimination of b gives:

$$K_1 C_1 = (1 + K_2 C_2) \frac{a}{1 - a}$$

When $C_2 = 0$ the equation represents the simple mass action equilibrium and is identical with the equation developed by Langmuir¹¹ and Hitchcock¹² to represent the adsorption of gases. This equation has been used to express oxygen uptake by hemoglobin, acetylcholine and epinephrine reacting for pharmacologic receptors, etc. The equation is applicable only with first order reactions, where the pharmacologic effect is directly proportional to the amount of drug combining with the receptors. It is

* Plant and bacterial cells are surrounded by an outer nonliving wall.⁹

known that the reaction is not always a first order reaction. Gaddum, for instance, has observed that the action of ergotoxine and atropine does not follow a first order reaction and that the following modification of the equation is necessary:

$$K_1 C_1 = 1 + (K_2 C_2)^n \frac{a}{1-a}$$

In this K_2 is the reciprocal of the concentration necessary to cause a doubling of C_1 .¹³

Since the type of physiologic or pharmacologic response and the degree of action elicited by a compound may be modified by a number of physical or physicochemical properties, the importance of such properties becomes apparent. Indeed, a systematic study of synthetic medicinals is scarcely profitable unless consideration is given to both the physical and chemical properties of the compounds in use.

SOLUBILITY AND PARTITION COEFFICIENTS

In homologous series of undissociated or slightly dissociated compounds¹⁴ in which the change in structure involves only an increase in the length of the carbon chain, gradations in the intensity of action have been observed for a number of unrelated pharmacologic groups of compounds, e.g., normal alcohols (antibacterial), alkyl resorcinols, alkyl hydrocupreines, alkyl phenols and cresols¹⁵ (antibacterial), esters of *p*-amino benzoic acid (anesthetics), alkyl 4,4'-stilbenediols¹⁶ (estrogenic), etc. It is well recognized that increasing the nonpolar portion of a molecule by increasing the length of a hydrocarbon side chain produces certain rather definite changes in the physical properties: the boiling point increases, solubility in water decreases, the partition coefficient increases, surface activity increases, viscosity increases, etc. Normally the lower members of an homologous series show a low order of activity; with the increasing length of the carbon chain (nonpolar portion of the molecule), the activity

increases, passing through a maximum. Further increase in the length of the carbon chain results in a rapid decrease in the activity. The increase in activity roughly parallels the decrease in water solubility and the increase in lipid solubility (partition coefficient). It may also be associated with an increase in surface activity. Changes of this type may be associated with the availability of the compound for the cell where the action occurs. It has been suggested¹⁴ that the observed decrease in activity with increasing length of the side chain may be due to the diminishing solubility of the compounds in water, or more precisely, the lowered solubility in the extracellular fluid in which the cell is immersed and which serves as a medium of transport to the cell surface. The observed decrease in activity may also be due to the lowered permeability of the cell membrane to molecules of increasing size.

The ω -phenyl substituted carboxylic acids illustrate the relationship of solubility, partition coefficients and antibacterial activity for an homologous series of compounds.¹⁷ Benzoic acid, although not truly a member of the homologous series, is included in Table 1 and Figures 1, 2, 3 and 4 for comparison. The series falls short of showing the length of the carbon chain necessary for decreased activity but it can be assumed that with continued increase in the length of the aliphatic side chain the activity will pass through a maximum then rapidly diminish. In homologous series of this type the polar (hydrophilic carboxyl group) remains constant and the nonpolar portion of the molecule (hydrocarbon) is increased. As a result of this type of change the water solubility decreases, lipid solubility increases and the partition coefficients increase as the series is ascended.

Table 1 shows the water solubilities, distribution coefficients and surface tension lowering of the acids.¹⁷ Graphically this data may be shown (Fig. 1) with the concentration plotted in terms of the molal con-

TABLE 1. THE RELATION BETWEEN CERTAIN PHYSICAL PROPERTIES OF HOMOLOGOUS ACIDS*

ACID	DISTRIBUTION		SURFACE
	SOLUBILITY†	COEFFICIENT‡	TENSION§
Benzoic	0.407	4.53	70.6
Phenylacetic	2.015	2.24	68.6
β-Phenylpropionic	0.934	5.26	65.8
γ-Phenylbutyric .	0.273	8.40	62.7
δ-Phenylvaleric ..	0.178	10.75	55.6
ε-Phenylcaproic .	0.048	17.80	46.4

* After Daniels, T. C., and Lyons, R. E.: J. Phys. Chem. 35:2049, 1931.
† Weight/weight in water at 30° C.
‡ Cottonseed oil/water.
§ 0.002 Moles N/500 solutions at 27° C. (water = 72.3).

centration of the acids (1/M) against the number of carbons in the side chain. The partition coefficients based on the data in Table 1 for the same series of acids is graphically represented in Figure 2. Figure 3 shows the surface tension of the acids in water at 27° C. for the same series of acids. In Figure 4 the bactericidal activities against *B. coli* expressed in 1/M concentration is shown for the acids.

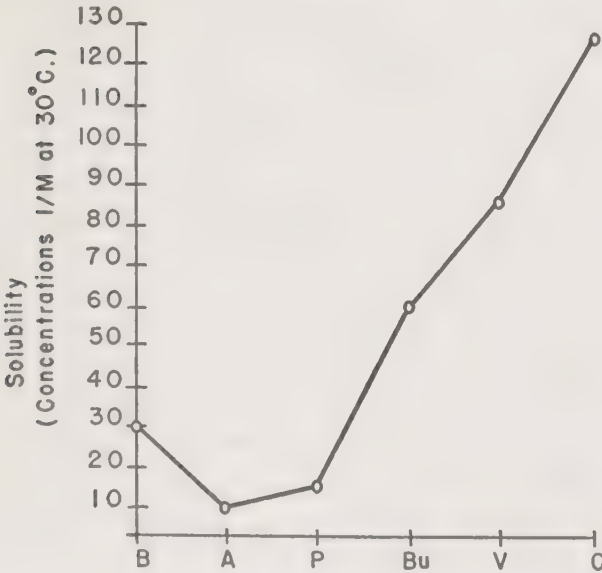


FIG. 1. Solubilities of certain acids in terms of normalities at 30° C. B = Benzoic, A = Phenylacetic, P = β-Phenylpropionic, Bu = γ-Phenylbutyric, V = δ-Phenylvaleric, C = ε-Phenylcaproic. (After Daniels, T. C., and Lyons, R. E.: J. Phys. Chem. 35:2052).

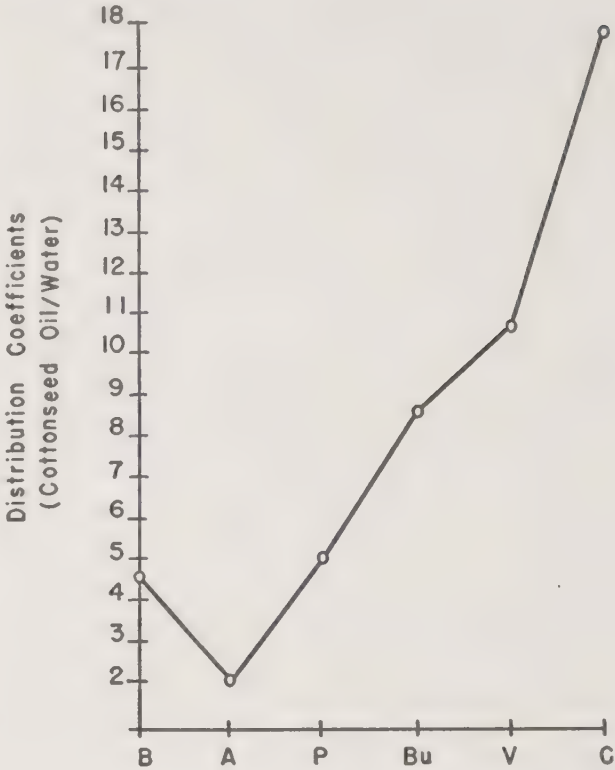


FIG. 2. Distribution coefficients of certain acids. B = Benzoic, A = Phenylacetic, P = β-Phenylpropionic, Bu = γ-Phenylbutyric, V = δ-Phenylvaleric, C = ε-Phenylcaproic. (After Daniels, T. C., and Lyons, R. E.: J. Phys. Chem.: 35:2054.)

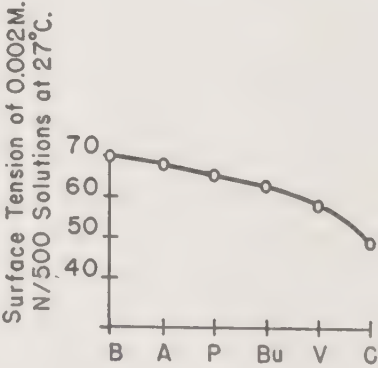


FIG. 3. Surface tension (in dynes/cm.) of N/500 solutions of certain acids at 27° C. B = Benzoic, A = Phenylacetic, P = β-Phenylpropionic, Bu = γ-Phenylbutyric, V = δ-Phenylvaleric, C = ε-Phenylcaproic. (After Daniels, T. C., and Lyons, R. E.: J. Phys. Chem. 35:2056.)

It is apparent from Figures 1, 2 and 4 that the solubilities of the acids and their partition coefficients (oil/water) closely par-

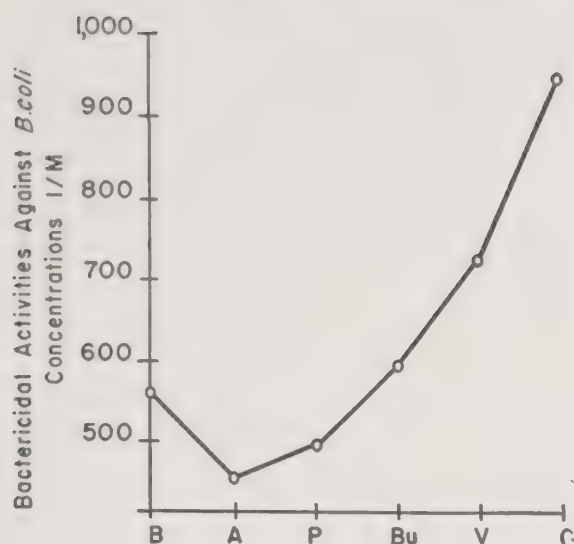


FIG. 4. Bactericidal value of certain acids against *B. coli*. B = Benzoic, A = Phenylacetic, P = β -Phenylpropionic, Bu = γ -Phenylbutyric, V = δ -Phenylvaleric, C = ϵ -Phenylcaproic. (After Daniels, T. C., and Lyons, R. E.: J. Phys. Chem. 35:2057.)

allel the observed bactericidal activities against *B. coli*. The same type of curve is shown for adsorption of the acids on activated charcoal.¹⁷ It should be noted (Fig. 3, Table 1) that the surface tension is lowered progressively as the series is ascended. This does not account for the low activity of phenylacetic acid in the series, and it must be inferred that surface activity in this series of compounds is not a primary factor that can be correlated with the antibacterial activity. It may, however, be a contributing factor.

The 4-*n*-alkylresorcinols (Table 2) and the *n*-alcohols (Table 3) also illustrate the relationship of biologic activity in homologous series differing only in the length of the carbon chain. The phenol coefficients of 4-*n*-alkylresorcinols against *B. typhosus* as determined by Dohme, Cox and Miller¹⁸ are shown in Table 2 and Figure 5.

Schaeffer and Tilley^{19,20} studied the same series of resorcinols and observed that the phenol coefficients for *Staph. aureus* continued to increase through the 4-*n*-nonylresorcinol. Braun and Schaeffer²¹ and Morgenroth and co-workers^{22,23} have observed that the optimum carbon length for antibac-

TABLE 2. PHENOL COEFFICIENTS OF 4-*n*-ALKYLRESORCINOLS*

4- <i>n</i> -ALKYLRESORCINOLS	<i>B. typhosus</i>
4- <i>n</i> -Propylresorcinol	5
4- <i>n</i> -Butylresorcinol	22
4- <i>n</i> -Amylresorcinol	33
4- <i>n</i> -Hexylresorcinol	45-56
4- <i>n</i> -Heptylresorcinol	30
4- <i>n</i> -Octylresorcinol	0

* After Dohme, A. R. L., Cox, E. H., and Miller, E.: J. Am. Chem. Soc. 48:1688, 1926.

TABLE 3. PHENOL COEFFICIENTS OF PRIMARY, SECONDARY AND TERTIARY ALCOHOLS*

PRIMARY NORMAL ALCOHOLS	<i>Eberthella typhosa</i>	<i>Staph. aureus</i>
Methyl	0.026	0.03
Ethyl	0.04	0.039
Propyl	0.102	0.082
Butyl	0.273	0.22
Amyl	0.78	0.63
Hexyl	2.3	
Heptyl	6.8	
Octyl	21.0	
SECONDARY ALCOHOLS		
Propyl	0.064	0.054
Butyl	0.152	0.131
Amyl	0.38	0.32
Hexyl	1.0	
TERTIARY ALCOHOLS		
Butyl	0.08	0.06
Amyl	0.18	0.14
Hexyl	0.45	

* After Tilley, F. W., and Schaffer, J. M.: J. Bact. Ref. (25) 12:303, 1926.

terial activity in the alkylhydrocupreines differs with the organism used. Thus, ethylhydrocupreine is stated to be the most active for pneumococci while the iso-octylhydrocupreine is most active for streptococci and *Corynebacterium diphtheriae* (*B. diphtheriae*). This variation in optimum activity of different organisms to members of an homologous series of compounds may be due in part to inherent differences (such as the degree of polarity) of the bacterial cell surface. It may also be due to differences in the permeability of the bacterial cell mem-

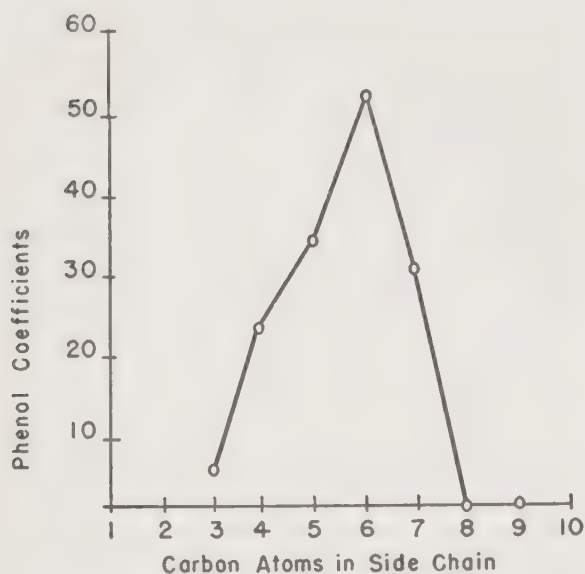


FIG. 5. Phenol coefficients of 4-*n*-alkylresorcinols against *B. typhosus*. (After Dohme, A. R. L., Cox, E. H., and Miller, E.: J. Am. Chem. Soc. 48:1869.)

branes to molecules of increasing size so that as the series is ascended the permeability is lowered. This might be referred to as a "dimensional factor," a term first coined by Alles²⁴ in connection with cholinergic drugs. The extent to which the above or other factors are involved is not known.

The branched chain alcohols (Table 3) are more water-soluble and have lower partition coefficients than the corresponding primary normal alcohols. Table 3 indicates that the branched chain alcohols are also less active as antibacterial agents. *n*-Hexyl alcohol is more than twice as active as the secondary hexyl alcohol and five times as active as the tertiary hexyl alcohol. The higher molecular weight alcohols (cetyl) are inactive as antibacterial agents and therefore the alcohols have the same type of curve as the alkylresorcinols against *Staphylococcus aureus*, e.g., activity increasing with increase in the length of the carbon side chain through a maximum. Esters of a number of aromatic carboxylic acids have been studied and it has been observed that as the carbon length of the alcohol is increased the activity rapidly increases.²⁶ The phenol coefficients of the esters of vanillic acid are

reported as follows: methyl, 1.7; ethyl, 7.3; *n*-propyl, 33.4. The isopropyl ester, which has a lower partition coefficient than the *n*-propyl ester, has a phenol coefficient of only 11.2.

The physical properties of some of the esters of *p*-hydroxybenzoic acid have been studied by Sabalitschka.²⁷ Table 4 shows the phenol coefficients, partition coefficients and dissociation constants of a series of the esters. It is apparent from Table 4 that the partition coefficients and observed antibacterial activity in this series of compounds are quite parallel.

TABLE 4. ESTERS OF *p*-HYDROXYBENZOIC ACID* (PHENOL COEFFICIENTS)

ESTER	Inhibition of Fermen- tation	<i>Staph.</i> <i>aureus</i> Bactericidal	Partition Coefficient†
Methyl	3.7	2.6	1.2
Ethyl	5.3	7.1	3.4
<i>n</i> -Propyl	25.0	15.0	13.0
<i>i</i> -Propyl	15.0	13.0	7.3
<i>n</i> -Butyl	40.0	37.0	17.0
Amyl	53.0	...	150.0
Allyl	15.0	12.0	7.6
Benzyl	69.0	83.0	119.0
Phenol	1.0	1.0	...

* After Sabalitschka, Th.: Pharm. Acta. Helv. 5:286, 1930.

† Lipoid/water.

The discussion of partition coefficients thus far has dealt largely with antibacterial agents. Historically, partition coefficients were first correlated with the biologic activity of hypnotic and narcotic drugs by Overton⁴ and Meyer.⁵ The importance of the physical properties of the central nervous system depressants is now generally recognized. Many of the compounds of this class, such as the volatile anesthetics, are relatively inert chemically.

The theory of narcosis, first expressed by Meyer in 1899, involved three postulates. As expressed by Falk²⁸ they are as follows:

1. All chemically indifferent substances which are soluble in fats and fat-like bodies must exert a narcotic action on living protoplasm in so far as they can become distributed in it.

2. The effect must manifest itself first and most markedly in those cells in which fatty or lipid substances predominate in the chemical structure and presumably in which they form essential participants of the cell function, viz., the nerve cells.

3. The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipid substances on the one hand, and for the remaining body constituents, i.e., principally water, on the other hand. Their efficiency is therefore dependent upon the partition coefficient which determines their distribution in a mixture of water and lipid substances.*

This theory has been substantiated in that excellent correlation between hypnotic activity and the partition coefficient has been observed^{29,30} for many compounds. It should be recognized that the theory relates only to the availability of the compound for the site of action and does not suggest a mechanism of action for the hypnotic drugs. Furthermore, it does not explain why all compounds with high partition coefficients do not show hypnotic properties, nor does it explain the hypnotic effect of compounds having negative partition coefficients, such as chloral hydrate.

Although the partition coefficients may be correlated with the observed biologic activity, it should be remembered that other properties are also involved and that the biologic action must be due to the over-all properties of the molecule and not to any one physical or chemical property.

THE EFFECT OF THE HYDROGEN ION CONCENTRATION ON THE BIOLOGIC ACTIVITY OF ACIDS AND BASES

Acids and bases may be responsible for biologic action as undissociated molecules or in the form of their respective ions. A great many compounds, particularly the weak acids and bases, appear to act as undissociated molecules. It is of course possible that a molecule may gain entrance to the cell where action occurs in the undissociated form and after reaching the site of action it may then function as an ion. Overton³¹ first pointed out that the free alkaloidal

bases showed greater penetrating power than their ionized salts. Osterhout³² established that hydrogen sulfide was absorbed by the cell as an undissociated molecule. Richardson and Shepard³³ observed that nicotine base is from four to six times as toxic for mosquito larvae as the ionized sulfate or hydrochloride salt. Hoskins³⁴ demonstrated arsenious acid is more effective as an insecticide in the undissociated form. Fantus³⁵ observed that 0.5 per cent cocaine solutions, alkalinized to give the free base, are equal in anesthetic activity to 5 per cent solutions of the cocaine hydrochloride. Rahn and Conn³⁶ studied benzoic, salicylic and sulfurous acids. In each case only the undissociated acids were significantly toxic for yeast. Rogers and Whittier³⁷ have shown that *Streptococcus lactis* ceases to make lactic acid when the concentration of undissociated lactic acid reaches 0.017 molar concentration, irrespective of the pH. Mandelic acid and many other organic acids are active antibacterial agents only in acid media and can be assumed to be absorbed as undissociated molecules. In general, the relation of activity to pH may be represented graphically as in Figure 6.

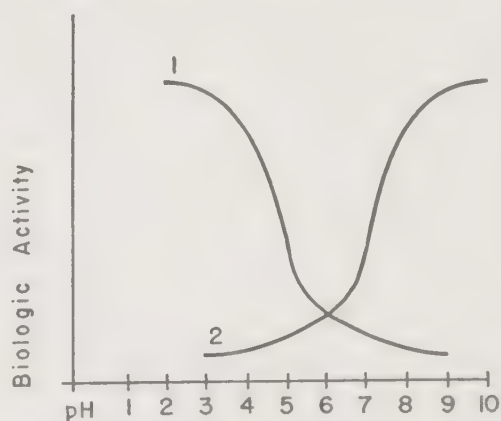


FIG. 6. Relationship between biologic activity and pH. (1 = acids; 2 = bases.)

The slope and pH at which the activity most rapidly falls or increases depends on the pK_a of the acid or base. The ion-base equilibrium of bases is graphically shown by Goyan.³⁸

* Falk, J. E.: Australian J. Science 7:48, 1944.

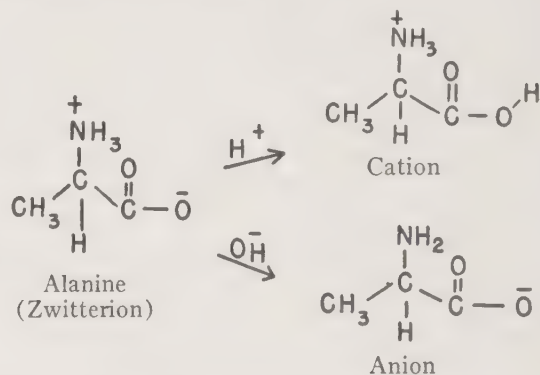
The antibacterial activity of benzoic acid, salicylic acid, mandelic acid and other acids of this type is greatest in acid media. The efficiency of these acids as antibacterial agents may be increased as much as one hundred times in going from neutral to acid solutions (pH 3).³⁶

The antibacterial action of the phenols is greatest at a pH below 4.5 and the activity again increases at a pH of 10 and above.³⁹

Hydrogen ion concentration modifies other properties as well as biologic activity. The solubility and partition coefficients of acids and bases may be greatly altered by changes in pH. Thus, cocaine hydrochloride is freely soluble in water (1:0.4), while the free base has only low water solubility (1:600). The solubility of the free base in chloroform, ether and vegetable oils, on the other hand, is rather high, and the partition between these solvents and water will favor the nonpolar solvents (high partition coefficients). Cocaine hydrochloride with its high water solubility is insoluble in ether and oils and other nonpolar solvents but is relatively soluble in chloroform because of the tendency of chloroform to form hydrogen bonds. The partition coefficients of the salt between water and all of the nonpolar solvents will, of course, be extremely low. The same is true in general for the salts of other acids and bases.³⁸ Changes in the hydrogen ion concentration will alter other physical properties of solutions containing acids or bases; surface tension will be altered because the pH determines the ratio of concentration of undissociated molecules (acids or bases) to the concentration of the corresponding ions. A solution of procaine hydrochloride, as an example, lowers the surface tension of water by only a few dynes per cm. Careful alkalinization of the solution progressively lowers the surface tension to the point where further addition of base produces precipitation. The surface tension of the solution will then increase. Changes of this type will also modify the intensity of biologic activity. The work of Fantus³⁵ on

alkalinized cocaine solutions illustrates this effect. The salts of acids or bases that are absorbed as undissociated molecules will develop their biologic activity in proportion to the concentration of free undissociated molecules in the solution. Thus, the time of onset of action and the intensity of action will vary with the concentration of undissociated molecules.

In addition to modifying the physical properties of solutions, changes in pH may also affect the reactivity of acidic and basic groups on the cell surface or within the cell.⁴⁰ At the isoelectric point, potential anions and cations in a protein or cell exist as "zwitterions." The effect of modifying the pH above or below the isoelectric point may be shown as follows:



Increasing the pH of the medium (which is the same as adding OH ions) will increase the concentration of the anions on the cell, thereby increasing the activity for biologically active cations. Decreasing the pH of the medium will increase the concentration of cations on the cell and thereby increase the activity for biologically active anions.

Active Ions. The mole percentage of a dissolved acid or base in the "acid" form may be readily calculated for any pH value from the mass law equation, as follows:

$$P = \frac{100}{1 + \text{antilog}(\text{pH} - \text{pK}_a)}$$

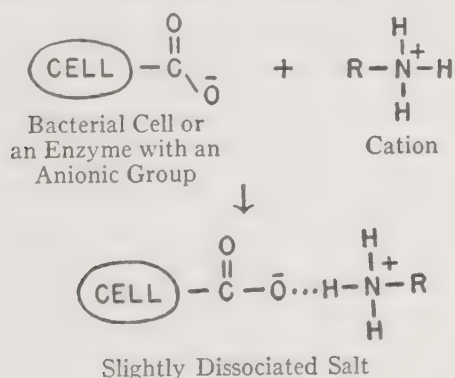
P = Mole per cent of acid or base in the "acid" form as defined by the Brønsted generalization. For weak acids, "acid" refers to the undissociated molecule; hence, for acids $(100 - P)$ represents the mole per cent in the ionic form. For weak bases, the corresponding "acid" form is the cation form,

and for weak bases, P represents the mole per cent of the base that exists in equilibrium in the ionized form.

pK_a = negative logarithm of the acid dissociation constant and is equal to the pH value at which the acid or base is 50 per cent ionized. (For bases in water solution, $pK_a = pK_w - pK_b$).

pH = the value at which the percentage in "acid" form is to be determined.

The per cent of ionization at the body pH (7.3) for a large number of acridine compounds has been recorded by Albert and co-workers.⁴¹ It was observed that a basicity sufficient to induce at least 75 per cent ionization at pH 7.3 at 20° C. (or 60 per cent at 37° C.) is necessary for effective antibacterial action in the series. It also was shown that the acridine cations are largely responsible for the activity. The undissociated molecules, anions or zwitterions have an insignificant effect on activity. A great many other compounds exert their biologic effect as ions. Stearn and Stearn⁴⁰ first postulated that the basic dyes (e.g., triphenylmethanes, acridines, etc.) function as antibacterial cations by reacting with essential anions (acid groups) of the bacterial cell to give slightly dissociated compounds. This may be illustrated by the following equation:



In this manner, functional groups of the organism can be blocked and cellular metabolism inhibited (bacteriostasis). This means that active compounds of this type must be relatively highly ionized at body pH. In the case of the acridines it has been shown⁴¹ that derivatives functioning as cations with a pK_a of less than 7.8 will be ineffective antibacterial agents. Albert⁴² refers to the large number of substances that show

TABLE 5. THE PERCENTAGE OF IONIZATION AT pH 7 IN RELATION TO BASIC STRENGTH*

pK_a OF BASE† (Brønsted)	pK_b OF BASE (Classical)	PERCENTAGE at pH 7
1	13	0.0001
2	12	0.001
3	11	0.01
4	10	0.1
5	9	1
6	8	9
7	7	50
8	6	90
9	5	99
10	4	100

* After Albert, A.: Australian J. Science 6:137, 1944.

† pK_a of base refers to the Brønsted generalization:



$$pK_a = \text{pH} + \log \frac{\text{acid}}{\text{base}} = \text{pH} + \log \frac{\text{NH}_4^+}{\text{NH}_3}$$

pK_a values may be calculated from classical pK_b values by the equation: $pK_a = pK_w - pK_b$, where pK_w is the log form of the dissociation constant of water (i.e. $pK_w = 14.0$ at room temperature, 13.5 at 40°C, etc.).

marked antibacterial activity "and yet have little else in common beyond possessing cations of high molecular weight (150 or more) and being completely ionized at pH of 7." Among these may be listed the aliphatic amines, quaternary ammonium compounds, diamines, amidines, diamidines, guanidines, biguanidines, phenazines, pyridinium compounds, etc. The similar biologic properties of compounds of this type led Albert⁴³ to suggest the new terms "kationic antiseptics" and "kationic chemotherapy." He has also ably restated the Stearns' hypothesis as follows:

Kationic chemotherapeutic agents seem to act through their cations competing with hydrogen ions for the same positions (anions) on a vital enzyme. This competition could be successful (e.g., toxic to the parasite) only when the molecular complexity of the drug is such that sufficient adsorption occurs significantly to favour retention of the drug in the face of continual assaults by hydrogen ions. Raising the pH value of the medium should assist the anti-parasitic effect by removing hydrogen ions, but when the pH approaches the pK_a of the drug, the ionization of the latter is interfered with so its action should decrease.*

* Albert, A.: Australian J. Science 6:137, 1944.

In the same manner that the quaternary ammonium compounds (invert soaps) function as biologically active cations, the ordinary soaps may function as anions. Their antibacterial activity, however, is extremely low. Less is known concerning the biologically active anions than the corresponding cations. In the first place, fewer of the anions show biologic activity, which may be due in part to the strong hydrophilic properties of the acid groups tending to give highly water-soluble compounds. Moreover, most bacteria are anionic in character at a pH of 7, having isoelectric points of approximately 4. Many, but not all, of the active sulfonamides are acidic in character but they do not appear to function as anions.⁴⁴ However, the maximum activity has been observed for those compounds that give 50 per cent ionization at the pH of the body.⁴⁵

It has been pointed out that in certain cases biologic activity increases with increased ionization. In other cases, where undissociated molecules are responsible for the biologic effect, the activity decreases with increased ionization. It should be kept in mind, however, that in the case of biologically active acids and bases the concentration of ions and undissociated molecules is determined by the pH value of the environment in which action occurs.

SURFACE ACTIVITY: ADSORPTION AND ORIENTATION AT SURFACES

Certain types of molecules have the property of concentrating and orienting in a definite configuration at the interface or surface of a solution and thereby lowering the surface energy. Such compounds are said to be positively adsorbed, and the energy relations may be expressed mathematically by the Gibbs adsorption equation.

$$\mu = -\frac{C}{RT} \frac{d\gamma}{dc}$$

This equation applies ordinarily to dilute solutions and the symbols represent the following:

- μ = Excess of the solute at the surface per unit area in relation to the concentration in the solution
- c = Concentration of solute in the solution
- R = Gas constant
- T = Absolute temperature
- γ = Surface tension in dynes/cm.

$\frac{d\gamma}{dc}$ = Rate of change of surface tension with concentration.

When the surface tension decreases with increasing concentration, μ is positive and the solute is said to be positively adsorbed. If γ increases with increase in c , then μ is negative and the solute is said to be negatively adsorbed. In general, compounds less polar than water will be positively adsorbed in water, and if the compound is more polar than water, it will be negatively adsorbed. There are three general classes of surface active agents: anionic compounds, such as the ordinary soaps; cationic compounds, including the aliphatic amines and quaternary ammonium compounds, and nonionic compounds such as the hydrophilic esters and ethers.

The orientation of surface active molecules at the surface of water or at the interface of polar and nonpolar liquids takes place with the nonpolar (e.g., hydrocarbon) portion of the molecule oriented toward the vapor phase or nonpolar liquid and the polar groups (e.g., $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{OH} \end{array}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, etc.) toward the polar liquid. Three forces are involved in orientations of this type, namely: Van der Waals' forces, hydrogen bonds and ion dipoles. Van der Waals' forces represent mainly the forces of attraction between the nonpolar groups tending to hold the hydrocarbon groups together. An aliphatic hydrocarbon chain of 18 methylene groups has an attractive force for another hydrocarbon chain of the same length (both in *trans* configuration) of approximately 15 K_g. cal. per mole. This force is of the same order of magnitude as an ion dipole association.⁴⁶ Oleic acid on water forms a mono-

molecular film in which the hydrocarbon chain tends to stand vertically on the water surface, pointing into the vapor of the solution, and the —COOH groups are pointed into the water. If mineral oil or another nonpolar liquid is now added to the water solution to form a liquid/liquid interface, the hydrocarbon chains of oleic acid will be pointed into the nonpolar mineral oil and the —COOH groups will remain in contact with the water. The oleic acid thereby tends to make the transition from the nonpolar to the polar phase less abrupt. In such cases, the free surface energy is greatly lowered. Benzene and water with sodium oleate as the solute, for example, gives free surface energies as low as 2 ergs per cm^2 .⁴⁷

Many, but not all, proteins will spread at air/water or oil/water interfaces and in doing so they form insoluble films. This change from a hydrophilic colloid to an insoluble film is thought to be due to an unfolding of the molecule. The student should refer to the classical papers on the constitution and fundamental properties of liquids by Langmuir^{48,49} and Harkins, Davies and Clark⁴⁷ for a detailed discussion of the orientation of molecules at liquid/vapor boundaries and liquid/liquid interfaces.

Surface activity has long been considered to be of significance in relation to the biologic properties of compounds. Traube⁵⁰ has shown that there is a marked parallel between the activity of a given class of depressant drugs (e.g., hypnotics, anesthetics) and their power to lower surface tension. It should be pointed out, however, that there are exceptions to the Traube rule (e.g., chloroform) and that the correlation holds for only members of a single chemical class. It should also be pointed out that the compounds to which the Traube rule applies are only mildly surface active. Compounds showing pronounced surface activity usually are unsuited for use in the animal body. Such compounds are lost through adsorption on proteins and they also have the undesirable feature of disorganizing the cell membrane

and producing hemolysis of red blood cells. In general, highly surface-active agents are limited in use to topical application as skin disinfectants or for the sterilization of inanimate objects such as instruments and rubber gloves. The surface-active cations of the quaternary ammonium type are used for this purpose. They are characterized by having a small hydrophilic cation attached to a long nonpolar group. Compounds of this type are nonspecific antibacterial agents, since they are adsorbed on all tissues as well as on bacteria. Their activity is greatly reduced by body fluids and by high molecular weight anions such as the ordinary soaps. In common with other surface-active substances, they tend to act destructively on denuded tissue. An important feature of the surface-active compounds is the property of "wetting" shown by their solutions. This property serves to bring the active agent into intimate contact with the total surface to which it is applied. This is, of course, a decided advantage for solutions intended for use as topical antiseptics.

The extent to which a compound lowers the surface tension of water has also been correlated with antibacterial activity for an homologous series of 4-*n*-alkylresorcinols.⁵² Although surface activity may be an important feature for certain type agents, it should be kept in mind that other physical properties may modify the activity in such a manner as to make the power of reducing the surface tension of no more than secondary importance. As an example, the surface tension of solutions of ω -phenyl substituted acids starting with benzoic acid (Fig. 3) is lowered constantly with increase in the length of the side chain. There is no apparent relation between the surface tension lowering effect and the observed bactericidal activities in the series (Fig. 4). On the other hand, the biologic activity closely parallels the partition coefficient and water solubility (Figs. 1 and 2). As pointed out by Schulman,⁴⁶ the surface activity of a compound "must be made

analogous to its drug action or biological action only at the interacting interface. The interfacial tension can change some 50-60 dynes/cm. for the same compound at interfaces composed of molecules varying only slightly in their chemistry."* As an example, a long chain alcohol, such as cetyl alcohol, is insoluble and inactive in water but can be dispersed readily when mixed with an equivalent number of moles of a long chain ion such as a soap. The long chain alcohol is adsorbed as a monolayer and can be shown to inhibit chemically the precipitation of soap by compounds normally producing precipitation. Moreover, the lytic properties of the soap are increased by as much as 100 per cent. If cholesterol is substituted for the aliphatic alcohol, inhibition of the lytic properties of the soap is obtained and there is no inhibition of the precipitation of soap compounds, therefore, a complete reversal of properties is observed. The enhanced lytic properties and the inhibition of precipitation of the soap is brought about by the presence of the long chain alcohol. This is due to the association of the nonpolar chain attached to the polar hydroxyl group with the nonpolar chain of the soap ion. If the hydroxyl group of the alcohol is esterified, the ester will show no effect on the properties of the soap solution. Schulman⁴⁶ also points out an interesting analogy between the behavior of the soap solution and that of bacteria. Organisms which are unaffected by a saponin solution undergo lysis with the same solution if the organisms previously have been incubated with a cholesterol solution.

In a series of long chain surface-active ions, Schulman and Rideal have observed that the lytic properties are related to the surface activity at a cholesterol or protein interface and not to the surface tension lowering of water.

Surface-active agents can be expected to have a pronounced effect on the permeability of the cell. This effect appears to be depen-

dent upon the degree of surface activity shown by the compound. Mildly surface-active agents may be adsorbed as a monolayer on the cell membrane and thereby interfere with the absorption of other compounds. On the other hand, highly surface-active agents may cause a distintegration or lysis of the cell membrane.

OXIDATION-REDUCTION POTENTIALS AND BIOLOGIC ACTION

The oxidation-reduction potential (redox potential) may be defined as a quantitative expression of the tendency a compound has to give or to receive electrons. It is related to the concentrations of the oxidant and reductant present under the conditions of the measurement and may be expressed mathematically by the following equation:

$$E_h = E'_o - \frac{0.06}{n} \log \left(\frac{\text{reductant}}{\text{oxidant}} \right)$$

E_h = The oxidation-reduction potential of the system being measured.

E'_o = The standard electrode potential at a specific hydrogen ion concentration.

n = The number of electrons transferred. 0.06 is a thermodynamic constant for 1 electron transfer at 30° C.

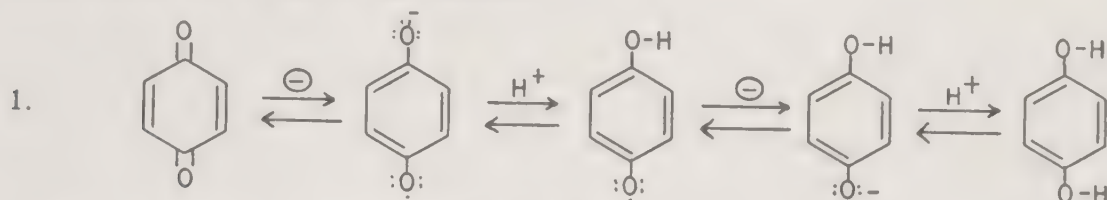
It should be noted that when the concentration of reductant equals the concentration of the oxidant, E_h is equal to E'_o .

The oxidation-reduction potential is referred to as the normal hydrogen electrode ($\frac{1}{2}H_2 = H^+ + e$), which is defined as having a zero potential. However, the calomel half cell is commonly used as the reference electrode and it is therefore necessary to correct for the potential which it contributes. Satisfactory E_h values can be obtained for only those oxidation-reduction systems that are reversible and ionic in character. Such reactions proceed at a rapid rate and give stable potentials.

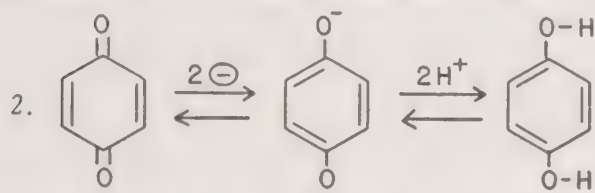
The equation used for measuring oxidation-reduction potentials applies in a general sense to the measurement of hydrogen ion concentration, and therefore, the pH of the oxidation-reduction system must be given

* Schulman, J. H.: Trans. Faraday Soc. 39:412, 1943.

consideration. The tendency of most compounds to be oxidized or reduced is greatly affected by the pH of the medium. Most oxidation-reduction systems will have anions (reduced form) which accept hydrogen ions and thereby alter the observed potential. As an example, the reduction of a quinone to the corresponding hydroquinone gives a phenol which can dissociate to give anions. The reduction involves the addition of two electrons which can be shown as follows:



There is evidence to indicate that the electron transfer takes place stepwise (reaction 1), in which case a semiquinone would be an intermediate state in the reduction or oxidation. Reaction 2 can occur in only



strongly alkaline solutions. The hydrogen ion concentration of the oxidation-reduction system can be incorporated in the equation (cf. Goyan⁵³) as follows:

$$E_b = E_o - \frac{0.06}{n} \log (H^+)^2 \left(\frac{\text{reductant}}{\text{oxidant}} \right)$$

Many organic oxidation-reduction systems involve two electron transfers; in this case the value of n is 2. Hydroquinone, as an example, forms a bivalent anion and its concentration can be expressed in terms of two dissociation constants. If the hydrogen ion concentration is much greater than either of the dissociation constants, then the total concentration of hydroquinone (reductant) is almost equal to the concentration of the undissociated molecules. The quantity E_o' differs from E_o in that the latter is constant with respect to pH, assuming an ideal reduction. On the other hand, E_o' has a different value for each pH value.

The oxidation-reduction potential may be compared to an acid-base reaction. The latter case may be regarded as the transfer of a proton from an atom in one molecule to the atom in another, while in the case of an oxidation-reduction reaction, there is an electron transfer. Since living organisms function at an optimum potential range which varies with the organism, it might be assumed that the oxidation-reduction

potentials of compounds of a certain type would correlate with the observed biologic effect.⁵⁴ However, there are a number of reasons why satisfactory correlations have not been observed. It should be kept in mind that the oxidation-reduction potential applies to a single reversible ionic equilibrium which does not exist in a living organism. The living cell is obliged to carry on a great many reactions simultaneously, involving oxidations of an ionic and nonionic character, some of which are reversible and others are irreversible. It is able to function normally by controlling the rates of reactions through established enzyme systems. The reactions of a reversible ionic character are perhaps comparatively small in number, and therefore it is not surprising to find poor correlation between oxidation-reduction potentials and biologic effect. Page and Robinson⁵⁵ have studied the relation between the bacteriostatic activity and the normal reduction potentials of substituted quinones. They find no simple relation between the reduction potentials (E_o') of 20 substituted quinones and their observed bacteriostatic activity. The quinones showing marked activity against *Staph. aureus* gave reduction potentials falling between -0.10 and $+0.15$ volts, with optimum activity associated with a potential of approximately $+0.03$ volts.

The same authors failed to find a similar relation between oxidation-reduction potentials of 18 commercially distributed oxidation-reduction indicators and their activity against *Staph. aureus*.

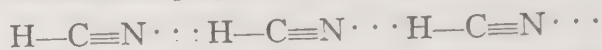
The reduction potentials of a number of acridines have been studied.⁵⁶ The more active compounds have an $E_{\frac{1}{2}}$ of less than -0.4 , but no detailed correlation with the observed antibacterial activity was observed.

At the present time, oxidation-reduction potentials are of the greatest importance in connection with the study of the kinetics of cellular metabolism, where they can be investigated for separate enzyme systems. Since redox potentials represent reversible ionic equilibrium reactions involving a transfer of electrons and the living cell functions with both reversible and irreversible reactions, one expects to find little or no correlation between drug action and their redox potentials.

HYDROGEN BONDING AND BIOLOGIC ACTION

The hydrogen bond,^{57,58} which is sometimes referred to as a hydrogen bridge, is a bond in which a hydrogen atom serves to hold two other atoms together. The hydrogen atom in such a bond is in a sense bivalent. The two bonds attached to hydrogen cannot both be covalent, for hydrogen has only one stable orbit and can form only one covalent bond. The other bond must be ionic. Consequently, the hydrogen bond is formed with electronegative atoms, which are those that form ionic bonds. In addition, the atoms capable of forming hydrogen bonds have at least one unshared electron pair together with a complete octet. These atoms include F, O, N, and to a lesser degree Cl and S. There is also evidence that hydrogen attached to a triply bonded carbon as in HCN,⁵⁹ acetylene, etc., and hydrogen attached to a carbon that is attached to three electronegative atoms, as in chloroform, may form hydrogen bonds. In the last two cases, another molecule with an oxygen,

nitrogen or fluorine atom to act as a receptor for the hydrogen must also be present to form hydrogen bonds. Hydrogen cyanide forms linear polymers of the type



held together by hydrogen bonds. The high solubility of acetylene in acetone appears to be accounted for only by assuming the formation of hydrogen bonds in which hydrogen is attached to both the oxygen of the acetone and carbon of the acetylene.

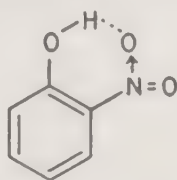
The strength of the hydrogen bond varies from 1 to 10 kg. cal. per mole and usually is about 5 kg. cal. per mole.⁶⁰ Thus, it is only about one tenth as strong as most covalent bonds, which range from about 35 to 110 kg. cal. per mole. In spite of the relative weakness of the bond it has a great effect upon the properties of substances. It has been shown to cause comparatively large changes in boiling points, melting points, heats of vaporization, solubilities, dielectric constants, infra-red absorption spectra and other properties.

The distance between two atoms held together by a hydrogen bond is considerably greater than the distance between the same two atoms held together by an ordinary chemical bond. Thus, the distance between oxygen atoms that are hydrogen-bonded varies from 2.5 to 2.8 Å, while the distance between the oxygen atoms in the oxygen molecule is 1.20 Å. On the other hand, the distance between hydrogen-bonded atoms is less than the distance between nonbonded atoms. Like ordinary chemical bonds, the strength of the hydrogen bond is an inverse function of the distance between the atoms.

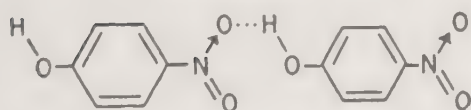
Phenomena formerly classified under association in many cases have been shown to result from hydrogen bond formation. Examples are the high boiling points of water and alcohols and the high molecular weights given by alcohols, carboxylic acids and amides when measured in nonpolar solvents. Hydrogen bonds play an important role in the structure of proteins, cellulose and certain plastics. Considerable evidence has

been accumulated to show that proteins are held in particular configurations by hydrogen bonds and that the denaturation of proteins involves the breaking of some of these bonds. It is significant that virtually all reagents that denature proteins are reagents capable of breaking hydrogen bonds.

The most common hydrogen bonds are the following: $\text{O}-\text{H}\cdots\text{O}$, $\text{N}-\text{H}\cdots\text{N}$, $\text{F}-\text{H}\cdots\text{F}$, $\text{O}-\text{H}\cdots\text{N}$ and $\text{N}-\text{H}\cdots\text{F}$. If such bonds occur within a molecule they are termed intramolecular, while if they occur between two molecules they are called intermolecular hydrogen bonds. Molecules are known that form both intramolecular and intermolecular hydrogen bonds simultaneously, an example being salicylic acid. *o*-Nitrophenol is an example of a molecule that forms an intramolecular hydrogen bond, while *p*-nitrophenol can form only intermolecular hydrogen bonds.



o-Nitrophenol



p-Nitrophenol

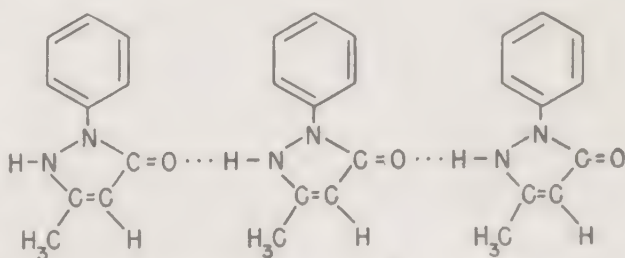
Intermolecular bonds are frequently much weaker than the intramolecular bonds.

In the above two cases the infra-red spectrum in carbontetrachloride solution shows the presence of a strong hydrogen bond with the ortho isomer, but no evidence of any hydrogen bonding with the para isomer. In the crystal, however, the para isomer probably forms hydrogen bonds, which account in part for its higher melting point as compared with the ortho isomer. The forming of intermolecular hydrogen bonds involves overcoming the kinetic energy (heat motion) of two molecules, while in the formation of intramolecular hydrogen bonds only the kinetic energy of part of one molecule is in-

involved. Strong intramolecular hydrogen bonds usually are found in five-membered rings (six-membered, counting the hydrogen atom).

In view of the profound effects the hydrogen bond has upon the physical and chemical properties of molecules, it is to be expected that correlation might be found between such bonds and biologic activity. Of course, the finding of such correlations is not proof that the hydrogen bond as such is directly responsible for observed differences in biologic activity. Concomitant or associated properties may be partly responsible, and the extent to which each property contributes to the over-all biologic action cannot be determined precisely. In a number of cases hydrogen bonding may be correlated with the observed biologic activity.

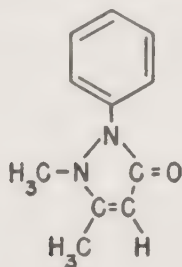
1-Phenyl-3-methyl-5-pyrazalene shows no analgesic properties; on the other hand, 1-phenyl-2,3-dimethyl-5-pyrazalene (antipyrene) is a well known analgesic agent. The former has a melting point of 127° C. and is comparatively insoluble at ordinary temperatures in water and very slightly soluble in ether. The latter has a lower melting point (112° C.) and is very soluble in water (1:1) and moderately soluble in ether (1:43). It is unusual for a methyl group to bring about such large changes. The effect appears to be best explained by the fact that the first compound can form hydrogen bonds of the type illustrated.



1-Phenyl-3-methyl-5-pyrazalene

The resulting large attractive forces between the molecules raises the melting point and lowers the solubility, especially in the non-polar solvents which are not capable of breaking the hydrogen bonds. On the other

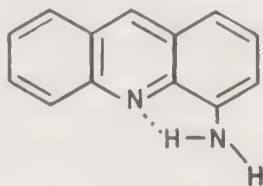
hand, the methyl compound can not form hydrogen bonds and has only comparatively weak attractive forces between its molecules.



1-Phenyl-2,3-dimethyl-5-pyrazalone
(Antipyrine)

Its melting point is lower in spite of its having a higher molecular weight and it has good solubility in nonpolar solvents.

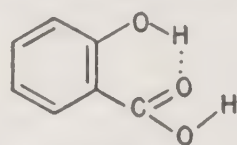
The five monoaminoacridines have been studied⁶¹ and their bacteriostatic activity was found to be related to their basic strength. The bacteriostatic activity is proportional to the extent of ionization at the biologic pH of 7.3.⁴¹ 4-Aminoacridine has virtually no bactericidal activity and abnormally weak basic properties compared with the others. This has been attributed to hydrogen bond formation between the two nitrogen atoms in the molecule.



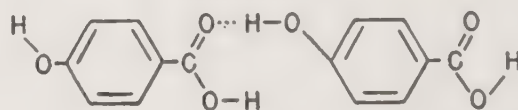
4-Aminoacridine

Salicylic acid (*o*-hydroxybenzoic acid) has quite an appreciable antibacterial action, but the para isomer (*p*-hydroxybenzoic acid) has an extremely low activity. The antibacterial activity of the esters is in the reverse order. Methyl salicylate, as an example, has an extremely weak antibacterial action, but methyl *p*-hydroxybenzoate (Nipagin) shows good action (cf. Table 4). A number of the esters of *p*-hydroxybenzoic acid are used as preservatives in various pharmaceutical and cosmetic preparations. The butyl ester (Butoben) is perhaps the most commonly employed. The difference in antibacterial

action of the free acids and their esters may be accounted for through hydrogen bond formation. It is also possible that hydrogen bonds may account for the pronounced differences in biologic action of the three isomeric monohydroxy benzoic acids. Only the ortho isomer (salicylic acid) shows analgesic and antipyretic properties. Likewise, salicylic acid is the only one of the three isomers that can form intramolecular hydrogen bonds. The *m*- and *p*-isomers can only form intermolecular hydrogen bonds.



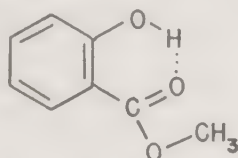
Salicylic Acid



p-Hydroxybenzoic Acid

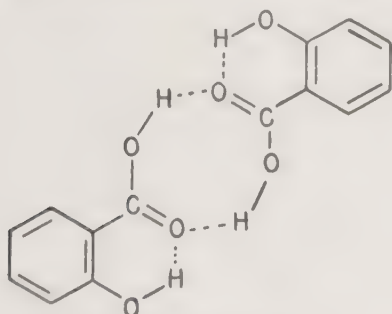
Salicylic acid is a much stronger acid ($K_a = 1 \times 10^{-3}$) than *p*-hydroxybenzoic acid ($K_a = 2.9 \times 10^{-5}$).⁶² The solubility of salicylic acid in water is less than that of *p*-hydroxybenzoic acid, but its partition coefficient (benzene/water, approximately 3) is much greater than that of *p*-hydroxybenzoic acid, which in the same solvents is approximately 0.001. The higher melting point of *p*-hydroxybenzoic acid may be associated with intermolecular hydrogen bonding, which can also account for the low partition coefficient and low bactericidal action. It should be noted that salicylic acid with an intramolecular hydrogen bond has the phenolic hydroxyl masked, but the carboxylic acid group is free and can function as an antibacterial agent similar to benzoic acid. *p*-Hydroxybenzoic acid, on the other hand, must form intermolecular hydrogen bonds leading to a high degree of association and thereby lowering its antibacterial activity. In the case of the esters of salicylic acid and *p*-hydroxybenzoic acid, the opposite effect in bactericidal power is observed. Methyl salicylate is without significant anti-

bacterial activity, but the esters of *p*-hydroxybenzoic acid show useful antibacterial properties. Methyl salicylate, through intramolecular hydrogen bond formation, has its functional group masked through hydrogen bonding as follows:



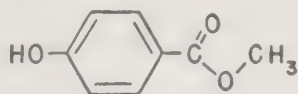
Methyl Salicylate

In solvents such as benzene and carbon tetrachloride, salicylic acid forms a dimer of the following structure:

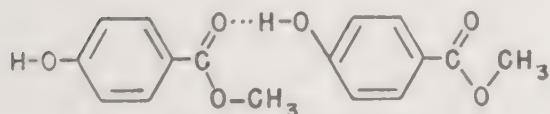


Salicylic Acid (dimer)

It has been shown from the infra-red spectrum that this dimer has its OH groups completely bonded. Methyl *p*-hydroxy benzoate and other esters of *p*-hydroxybenzoic acid, on the other hand, can form only intermolecular hydrogen bonds, which may be illustrated with the following structures:



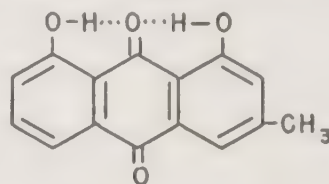
Methyl *p*-Hydroxybenzoate



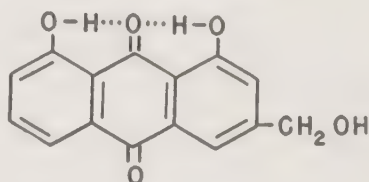
Methyl *p*-Hydroxybenzoate

Association through hydrogen bonding to form the dimer or higher polymers may occur, but the partition coefficient and antibacterial activity data shown (Table 4) for the esters of *p*-hydroxybenzoic acid indicate that the association is not high and that they may function as substituted phenols.

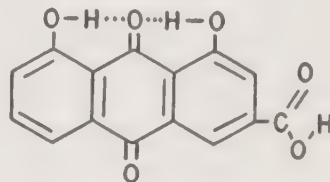
Many of the naturally occurring hydroxy anthraquinones undergo intramolecular hydrogen bonding. The following compounds are examples: Chrysophanic acid (1,8-dihydroxy-3-methyl anthraquinone), aloemodin (1,8-dihydroxy-3-carbinol anthraquinone), rhein (1,8-dihydroxy-3-carboxy-anthraquinone) and emodinanthrone (1,6,8-trihydroxy-3-methyl anthrone).



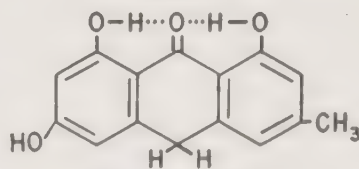
Chrysophanic Acid



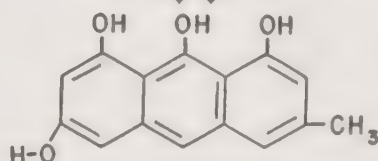
Aloe-emodin



Rhein



Emodinanthrone

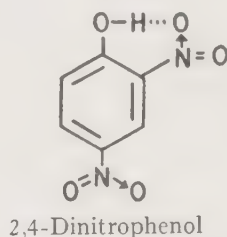
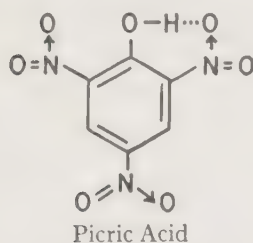


Emodinanthranol

The double intramolecular hydrogen bonding occurring in the 1,8-dihydroxy-anthraquinones is made possible by the carbonyl oxygen acting as a receptor for two hydrogen bonds. In the case of the tautomeric equilibrium of emodinanthrone $\rightleftharpoons$ emodinanthranol, it can be expected that hydrogen bonding will shift the equilibrium more toward the keto form. It is of interest that virtually

all of the naturally occurring anthraquinone drugs employed as cathartics have most of their phenolic hydroxyl groups masked through hydrogen bonding.

The nitrophenols, such as picric acid and 2,4-dinitrophenol, form intramolecular hydrogen bonds as follows:



The alcohols tend to form relatively strong hydrogen bonds and this property is thought to be associated with their ability to denature proteins.

It appears quite possible that certain types of biologically active molecules may first attach themselves to the site of action in the organism (such as the functional group of an enzyme system) through the initial formation of a hydrogen bond. Indeed, such bonding might in some cases be primarily responsible for the observed biologic effect. Molecules may, of course, have more than one hydrogen bond as a cross link where two or more hydrogen bonds are involved in the same reacting molecules. The distances between the electron bonding and reactive hydrogens of the drug and substrate must coincide to give the multiple bonding. Such linkages are, of course, quite specific.⁶³

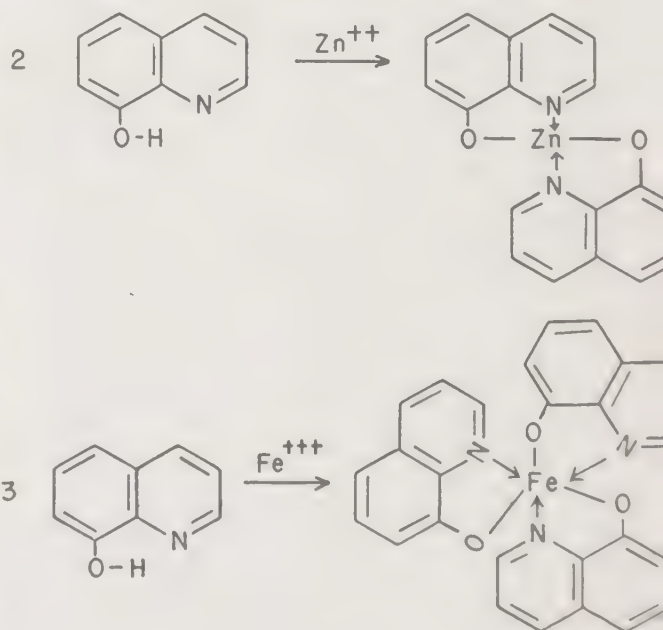
As more detailed knowledge is obtained in regard to living organisms, the relation of the hydrogen bond to biologic activity will be more clearly understood.

CHELATION AND BIOLOGIC ACTION

The term *chelate* was first applied by Morgan and Drew⁶⁴ to those compounds that combine with metals to form weakly dissociated complexes in which the metal is part of a ring. Such complexes are usually only sparingly soluble in water and freely soluble in organic solvents.

The metals of principal biologic interest are calcium, cadmium, cobalt, copper, iron, lead, magnesium, manganese and zinc. The important role of various metals in metabolism is well recognized but poorly understood. Zentmyer⁶⁵ and Albert⁶⁶ independently suggested that oxine (8-hydroxyquinoline) may act on fungi and micro-organisms by combining with trace metals essential for metabolism. Later Albert, Rubbo, Goldacre and Balfour^{67,68} prepared and made a bacteriologic study of 43 compounds related to oxine. A definite correlation between bactericidal activity and chelating power was observed. It is suggested that the active members of the series function by combining with the trace metals essential for bacterial growth. Not all of the chelating compounds studied showed antibacterial action. Activity was largely restricted to compounds closely related to oxine. The configuration of the molecule as well as other properties may contribute to the activity.

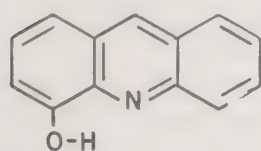
When oxine chelates with a divalent or trivalent metal, compounds having the following structures are formed:



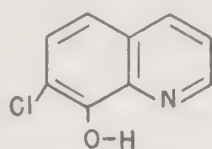
Comparatively little is known about the trace metal requirements of micro-organisms. Albert,⁶⁹ after exposing gram-positive and gram-negative organisms to lethal con-

centrations of oxine, attempted to restore the organisms to life by the addition of traces of different metals. Cobalt proved to be specific for the resuscitation of gram-positive organisms. Gram-negative organisms were restored more promptly by copper or zinc.

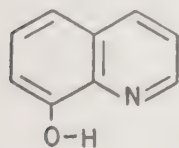
Although many organic compounds have chelating properties, not all such compounds have antibacterial activity. The compounds showing antibacterial activity thus far studied are closely related to oxine. Some of the more active compounds of interest are the following:



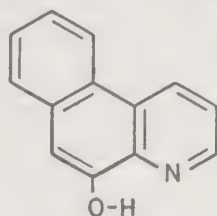
4-Hydroxyacridine



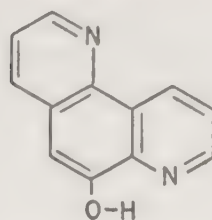
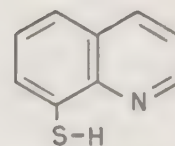
7-Chloro-oxine



Oxine



5,6-Benzo-oxine

6-Hydroxy-*m*-phenanthroline8-Mercaptoquinoline
(Quinoline, 8-thiol)

Thus far the chelating compounds have shown little or no evidence of specificity for the various metals, but they do represent an extremely interesting group of biologically active agents.

STERIC RELATIONSHIPS AND DRUG ACTION

The idea that steric or spatial relationships play an important role in drug action is not new. Ehrlich's lock and key theory proposed many years ago was a picturesque way of suggesting the importance of steric factors.

Many cases are known in which structural isomers have different biologic activities. In fact it is the rule rather than the exception

TABLE 6.—CHELATING COMPOUNDS*
(Highest Dilution Expressed as 1/M Preventing Visible Growth in 48 Hours
at 37° C Medium: Broth pH 7.3)

COMPOUNDS	ORGANISMS						METALS CHELATED AT pH 7.3	
	<i>Cl.</i> <i>Welchii</i>	<i>Str.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>B. coli</i>	<i>Proteus</i> <i>sp.</i>	<i>Ps.</i> <i>pyocyanea</i>	Strongly	Less Strongly
Oxine	100,000	100,000	100,000	1,600	800		Mn,Zn,Cd Co,Pb,Cu	Fe
7-Chloro-oxine	200,000	100,000	26,000	1,600	1,600		Mn,Zn,Fe, Cd,Co,Pb, Cu	
4-Hydroxyacridine .	16,000	8,000	4,000				Mn,Zn,Pb, Cu	Fe,Co
5,6-Benzo-oxine ...	400,000	200,000	26,000				Mn,Zn,Fe, Cd,Co,Pb, Cu	
6-Hydroxy- <i>m</i> - phenanthroline ..	200,000	100,000	26,000				Mn,Zn,Fe, Cd,Co,Pb, Cu	
8-Mercaptoquinoline	200,000	200,000	<3,000	<3,000	<3,000	<3,000	Co,Cu	Mn,Zn,Fe,Cd,Pb

*Modified after Albert, A., Rubbo, S. D., Goldacre, R. J., and Balfour, B. G.: Brit. J. Exper. Path. 28:73-75, 1947.

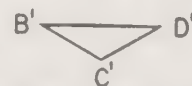
that this is the case, as would be expected from the fact that isomers of this type have different physical and frequently different chemical properties.

The geometric isomers (*cis-trans*) likewise have different physical and chemical properties and consequently should have different physiologic activities. Although the *cis-trans* isomers have not been extensively investigated from this standpoint, available reports⁷⁰ indicate they have different biologic activities.

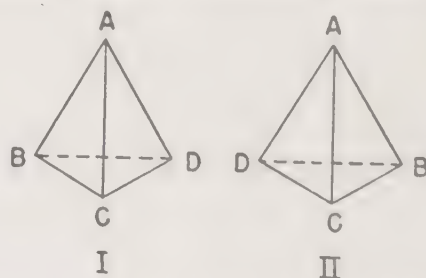
In the case of the optical isomers, the distereo-isomers differ from each other in physical properties, but since they have the same functional groups, they can undergo the same types of chemical reactions. However, the rate of these reactions may be quite different. Hence, here again distereo-isomers would be expected to have different biologic properties and such is borne out by experiment. Optical enantiomorphs, also called optical antipodes (mirror images), however, present a very different case for they are compounds whose physical and chemical properties are identical except for their ability to rotate the plane of polarized light. Here one might expect the compounds to have the same biologic activity. Such, however, is not the case with many of the enantiomorphs that have been investigated.

As examples of compounds whose optical isomers show different activities may be cited the following: *l*-hyoscyamine is 15 to 20 times more active as a mydriatic than *d*-hyoscyamine; *l*-hyoscine is 16 to 18 times as active as *d*-hyoscine; *l*-epinephrine is 12 to 15 times more active as a vasoconstrictor than *d*-epinephrine; *d*-norhomoepinephrine is 160 times more active as a pressor than *l*-norhomoepinephrine; *l*-ephedrine has about three times the pressor activity of *d*-ephedrine; *l*-synephrine has 60 times the pressor activity of *d*-synephrine; *l*-amino acids are either tasteless or bitter while *d*-amino acids are sweet; *l*-ascorbic acid has good antiscorbutic properties while *d*-ascorbic acid has none.

Although it is well established that optical antipodes have different physiologic activities, there are different interpretations as to why this is so. In fact, if one recalls that physiologic properties stem solely from the physical and chemical properties of substances and that optical antipodes have identical physical and chemical properties except for their ability to rotate the plane of polarized light, it may at first sight appear strange that there should be any difference in the physiologic action of optical antipodes. Cushny⁷¹ accounted for this difference by assuming that the optical antipodes reacted with an optically active compound in the body to produce diastereo-isomers with different physical and chemical properties. Easson and Stedman,⁷² taking a somewhat different view, point out that optical antipodes can in theory have different physiologic effects for the same reason that structural isomers can have different effects, i.e., because of different molecular arrangements, one antipode can react with a hypothetical receptor while the other cannot. Assuming a receptor



in tissues to which a drug can be attached and have activity only if the complementary parts B, D, C are superimposed, it is apparent that of the two enantiomorphs only I can be so superimposed. Under these conditions, I therefore would be active and



II would show no activity. This interpretation in a sense is not greatly different from that given by Cushny because the receptor has a unique configuration not much different from that of an optically active compound. Both theories demand a struc-

ture of unique configuration in the body, but in the one theory only one enantiomorph reacts while in the other they both react with one combination having greater biologic activity than the other.

In recent years the work of Pauling and his co-workers has shown the importance of steric factors in the combination of antibodies with haptens⁷³ and antigens.⁷⁴ They have shown that the shape of the hapten is a major factor in determining its inhibiting power, other factors being the polarizability of groups and the distribution of charge. They state: "... that the forces of attraction between antibody and antigen are interatomic forces operating through distances of a few angstroms and that the specificity of the resultant integrated attraction depends upon a detailed complementariness in structure of antibody and antigen."*

A theory in regard to sex hormonal activity based on steric factors has been proposed by Schueler⁷⁵ who states:

A given substance may be estrogenic if it consists of a rather large, rigid and inert molecular structure with two active hydrogen bond-forming groups (e.g., phenolic hydroxyl groups) located at an optimum distance of 8.55 Å from one another. If the active groups are at a distance of approximately 9-10 Å and are of somewhat weaker hydrogen bond-forming character (e.g., secondary alcoholic hydroxyl groups), then the substance may have androgenic activity.†

One difficulty with this theory is the behavior shown by triphenylethylene, triphenylchloroethylene, tetraphenylethylene, diphenylethane and tolane. The first two compounds have good estrogenic activity, while the last three are inactive in 100 mg. doses. None of these compounds has hydrogen atoms that would normally be expected to form strong hydrogen bonds. Certainly, the ability of the para hydrogen atoms in triphenylethylene and triphenylchloroethylene to form hydrogen bonds is much less than the ability of the hydroxyl in a secondary alcohol to form hydrogen bonds. Also,

there would be virtually no difference in the ability of the para hydrogen atoms in triphenylethylene and tetraphenylethylene to form hydrogen bonds. In spite of this shortcoming of the theory, the steric factor may be of considerable importance in the activity of estrogens and androgens.

Recently, Pfeiffer⁷⁶ collected some data on a number of compounds from which he concludes that parasympathomimetic stimulant action depends on having two adjacent oxygen atoms at distances of approximately 5.0 Å and 7.0 Å from a methyl group or groups attached to nitrogen.

Since these compounds (acetylcholine, metacholine, urecholine, etc.) do not have rigid structures, the actual distance between the oxygen and methyl groups will vary. Actually, the molecule can be bent around until the oxygen atoms touch the methyl groups on the nitrogen. The distances given are presumably those where the oxygens are at the maximum distance from the methyl groups. Since the molecule has this flexibility, these distances may be of no significance as far as indicating the distances between receptors on the cell surface, as it is not known whether the molecule is fully extended when attached to the cell.

The fact that β -diethylaminoethyl acetate and β -diethylaminoethyl propionate⁷⁷ show this same stimulant action would indicate that a methyl group need not necessarily be attached to the nitrogen. These two compounds have adjacent oxygen atoms at a maximum distance of approximately 5 Å and 7 Å from the methylene groups on the nitrogen. In fact, one might suspect that the important distance is that between the oxygen atoms and the nitrogen atom, since the latter has the positive charge which would be expected to serve as a point of attachment to the cell through ion-ion or ion-dipole attraction.

Alles²⁴ has pointed out the importance of a "dimensional factor" with regard to the activity of cholinergic drugs.

* Pressman, D., Bryder, J. H., and Pauling, L.: J. Am. Chem. Soc. 70:1352, 1948.

† Schueler, F. W.: Science 103:221, 1946.

RESONANCE AND BIOLOGIC ACTION

A molecule that cannot be described accurately by a single valence bond structure but has an intermediate structure requiring two or more valence bond structures for its accurate description is said to be a resonating molecule or a resonance hybrid. Like any hybrid, a resonance hybrid partakes of the properties of the two or more forms from which it may be considered to have been derived. It is not to be regarded as a mixture of these forms but rather as a single substance having greater stability than any one of the contributing forms.

Resonance is associated with many of the physical and chemical properties of molecules. Since the latter determine biologic properties, correlations may be found between resonance and observed biologic activities. At present, correlations of this type are of a qualitative nature.

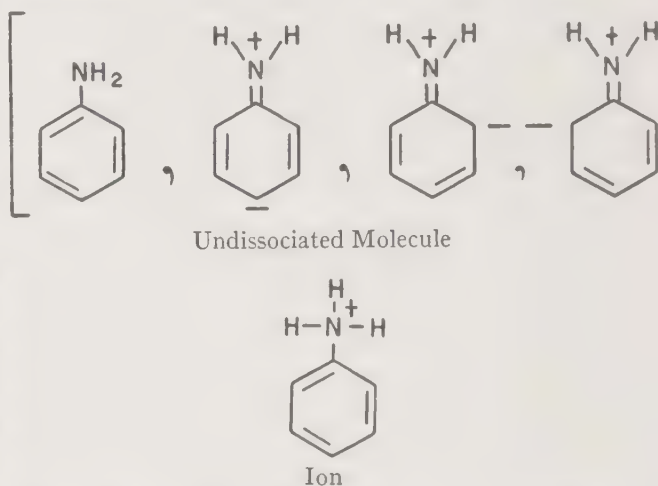
Examples where resonance alters the physical and chemical properties of molecules are discussed in detail in books on physical organic chemistry.^{58,78,79} Some of the properties that have been shown to be affected by resonance are acid strength, basic strength, oxidation-reduction potential, absorption spectrum, dipole moment, solubility, partition coefficient, tautomerism and rate of reaction. It is apparent, therefore, that resonance will affect the biologic activity of a great many types of compounds either directly or indirectly through the modification of the above properties.

The K_a 's of carboxylic acids, judging only from the K_a 's of alcohols and the effect of the carbonyl group on the strength of alcohols, should be of the order of 10^{-12} to 10^{-14} . The fact that the carboxylic acids have K_a 's around 10^{-5} is mainly due to resonance. The ion has contributions from

two forms of equal energy ($\text{R}-\overset{\text{O}}{\underset{\text{O}^-}{\parallel}}\text{C}-\text{O}^-$, $\text{R}-\overset{\text{O}^-}{\underset{\text{O}}{\parallel}}\text{C}=\text{O}$), while the undissociated acid

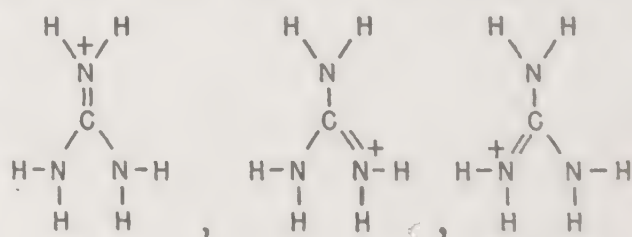
has contributions from forms of unequal energy ($\text{R}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{H}$, $\text{R}-\overset{\text{O}^-}{\underset{\text{O}^+}{\parallel}}\text{C}=\text{O}-\text{H}$). Since forms with equal energy give the maximum stabilization, the ion is stabilized with respect to the undissociated molecule by the resonance, and hence the acidity is increased as a result of the resonance.

Aniline and other aromatic primary, secondary and tertiary amines are examples of cases in which the basicity of compounds is decreased because of resonance. Here, the undissociated molecule is stabilized by resonance while the ion has no resonance stabilization.

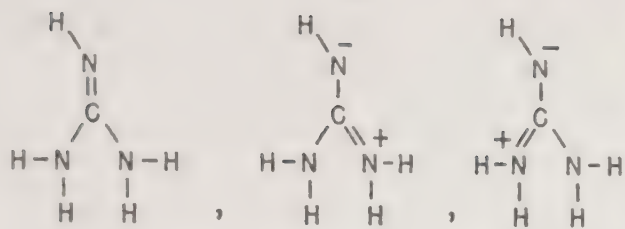


No other forms are possible in the ion because the nitrogen already has four bonds and a positive charge and hence cannot interact with the ring. The resonance weakens the compound as a base because the undissociated molecule is stabilized more than the ion.

A case in which resonance increases basicity is that of guanidine, in which the ion is stabilized by three forms of equal energy,

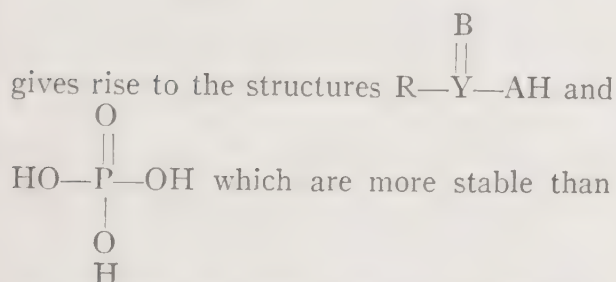
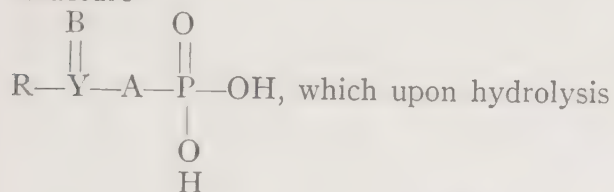


whereas the undissociated molecule has contributions of forms of unequal energy.



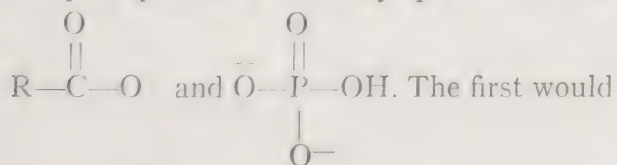
The ion is greatly stabilized with respect to the undissociated molecule. Hence the resonance increases the basicity of the compound. Guanidine is a very strong base, comparable to sodium hydroxide.

Kalckar⁸⁰ has used resonance to account for the behavior of the phosphorous compounds which supply the driving force for many biologic syntheses. These compounds have high energy phosphate bonds and are divided into four classes: pyrophosphates, carboxyl phosphates, enolic phosphates and guanidine phosphates. They all have the structure

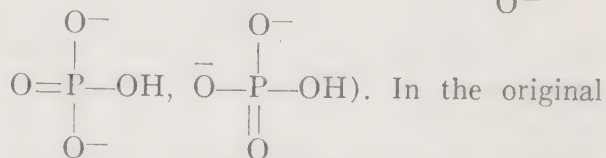
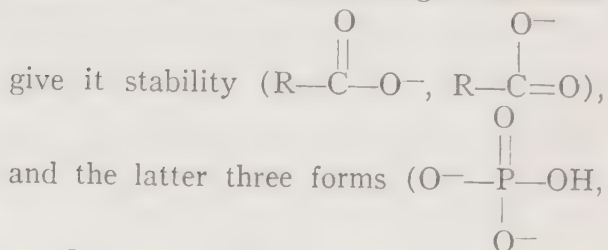


the original structure. The bond, which is written as a double bond, between phosphorus and oxygen, is not a true covalent double bond but has some semipolar double

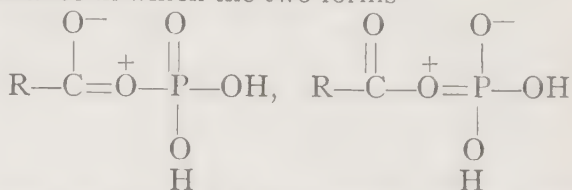
bond character $-\overset{\text{O}^-}{\text{P}^+}-$. However, it is written as a double bond to demonstrate more clearly the resonances involved. Taking a carboxyl phosphate as an example, the hydrolysis products at body pH would be



have two equivalent resonating forms which



molecule there is a condition of opposed resonance in which the two forms



both tend to put a plus charge on the same oxygen atom. The two forms are mutually exclusive, however, because insofar as the first succeeds, the second will fail, since the oxygen has a limited capacity for holding the plus charge. The net effect of this opposed resonance is that the molecule is stabilized very little, if any, and it therefore has high energy compared with its hydrolysis products. In the case of pyrophosphates, both A and B are oxygen, as in the above case. With guanidine phosphate, both A and B are nitrogen. Thus, in each of these cases, A and B are the same and hence that part of the hydrolysis product containing A and B will have resonance forms of equal energy which leads to high stability. With enolic phosphate, A and B are different, but here the hydrolysis product is stabilized by a tautomeric shift to the keto form.

The aminoacridines have been investigated from the standpoint of ionic resonance and antibacterial activity by Albert and co-workers.⁴¹ They found that antibacterial activity was correlated with the basicity of the compounds and the basicity was associated with ionic resonance. Since they were able, however, to make some compounds of good activity which had no ionic resonance but high basicity, and other com-

pounds of virtually no activity with much ionic resonance but low basicity, it appeared that ionic resonance is not as fundamental a property for activity as basicity. These authors take the view that both basicity and ionic resonance may play a direct but interdependent role in antibacterial activity.

It has been pointed out⁴⁴ that all the active sulfonamides are resonating structures in which the amino group tends to become coplanar with the ring, to assume a plus charge and to be doubly bonded to carbon. Most of the inactive or slightly active compounds have structures in which the resonance is decreased.

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3

Metabolic Changes of Drugs and Related Organic Compounds in the Body (Detoxication)

GENERAL CONSIDERATIONS

SITE OF DETOXICATION

CHEMICAL CHANGES OF DRUGS IN THE
GASTRO-INTESTINAL TRACT

DETOXICATION REACTIONS

HYDROCARBONS

ALCOHOLS

ALDEHYDES

KETONES

ACIDS

ESTERS

AMINO COMPOUNDS

NITRO COMPOUNDS

PHENOLS

SEX HORMONES

GENERAL CONSIDERATIONS

This chapter is intended to orient the student on some of the chemical changes foreign substances, particularly drugs, undergo in the body. The metabolic changes involved are commonly referred to as "detoxication" or "detoxication mechanisms." The subject is complicated and at the present time is not subject to precise treatment. Much of the literature on detoxication is of a qualitative nature and serves at best to indicate some of the common reactions that occur in the animal body. The terms "detoxication" or

"detoxication mechanisms" persist in the literature to cover the general aspects of the subject despite the fact chemical changes are involved that may or may not relate to detoxication. Many compounds foreign to the body are nontoxic, and moreover, some of the intermediates formed in the body are more toxic than the parent compound from which they are derived. i.e., arseno compounds are cleaved in the body and converted to the corresponding "arsine oxides" (cf. compounds of arsenic).

Although not all metabolic changes lead

to compounds of lower toxicity, in general, when chemical changes occur, the substances finally excreted are usually less toxic than the compound administered. It is apparent, therefore, that detoxication is involved in the process of excreting many foreign substances.

A great many compounds foreign to the body have been observed to pass through the body without undergoing any appreciable change. For the most part, these compounds appear to belong to one of two general classes.

1. Compounds that are insoluble in the body fluids and normally show no significant biologic action other than the physical effect (solvent, mechanical, etc.) they may exert on the tissues and fluids with which they come in contact. Examples are mineral oil and barium sulfate.

2. Compounds that are freely soluble in body fluids, relatively insoluble in the immiscible solvents and resistant to oxidative change. Compounds of this type, with the notable exception of the active cations and anions, are usually relatively nontoxic and rapidly excreted. Examples of this type are the aromatic and aliphatic sulfonic acids and certain of the carboxylic acids, such as mandelic acid, etc.

The detoxication of substances in the body is known to include a number of different mechanisms and perhaps as many different enzyme systems. For the most part the process appears to involve the conversion of a relatively nonpolar molecule (low water solubility) into a more polar molecule. Expressed in term of solubilities and partition coefficients this over-all change represents the conversion of substances poorly soluble in body fluids into substances more soluble or freely soluble in body fluids.

It follows, therefore, that toxic substances having relatively high partition

$$\text{coefficients } \left(\frac{S \text{ (immiscible solvent)}}{S \text{ (water)}} = P \right)$$

will tend to be converted into compounds having lower partition coefficients and

lower toxicity. This may be accounted for by the assumption that those compounds having high partition coefficients (relatively poor solubility in body fluids) are more available to the cell, where conjugation and other types of chemical changes may occur to form compounds having lower partition coefficients (greater solubility in the body fluids) which are then excreted.

Quick¹ associates the detoxication process with the conversion of "a weak acid which the body cannot excrete to a strong acid which it can eliminate." While acid strength may be an important factor, it does not appear to be the sole determining factor in the detoxication process. As an example, benzoic acid ($K_a 6.5 \times 10^{-5}$) has a partition coefficient (ether/water) of approximately 30 and is excreted by man largely as hippuric acid ($K_a 2.3 \times 10^{-4}$), which has a partition coefficient in the same solvents of less than 0.4. Thus, while the acid strength of hippuric acid is more than three times greater than that of benzoic acid, its partition coefficient is less by a factor of 75. Gentisic acid (2,5-dihydroxybenzoic acid) has an acid strength ($K_a 1.03 \times 10^{-3}$) more than four times greater than hippuric acid, yet is excreted largely as the sulfate. Gentisic acid has a partition coefficient (ether/water) of approximately 12, and although the partition coefficient of gentisic acid sulfate does not appear to have been measured, it can be assumed to be extremely low.

In addition to acid strength and partition coefficient, a number of other factors that may determine the degree and type of chemical change foreign compounds undergo in the body appear to be involved. Among these may be mentioned surface activity, functional groups, steric effects and other properties that may affect the availability of the molecule for the cell where reaction occurs. Moreover, the extent to which a reaction may occur depends on a number of other variable factors, for example, concentration, speed of the reaction and rate of excretion.

In general, toxic compounds tend to un-

dergo chemical change. The introduction of a carboxyl or other acidic (solubilizing) groups into phenols, piperidine compounds and other biologically active molecules tends to lower the toxicity. An interesting illustration of this effect is afforded by some of the ester drugs such as atropine, cocaine, procaine, arecoline, etc., all of which are biologically active and toxic until hydrolysis occurs. The acids and amino-alcohols formed from the hydrolysis are, without exception, relatively nontoxic. Likewise, the hydrolysis products have lower partition coefficients than the esters from which they are obtained.

It has been observed² that the phenylacetyl derivatives of glutamine, glycine and ornithine when fed to man, dog and fowl are excreted unchanged, irrespective of the type of conjugation phenylacetic acid undergoes in the animal to which the derivative is administered. The fact that this species difference does not apply to the conjugates may indicate that the conjugated compounds, because of their physical properties, are not available at sites of action where degradation and re-conjugation may occur.

The chemical changes compounds undergo in the body are of considerable interest and frequently of great practical value in the search for new and improved medicinals. The discovery by French workers³ that the azo dye Prontosil, which is inactive in vitro, is converted by reduction in the body to the active sulfanilamide led to the rapid de-

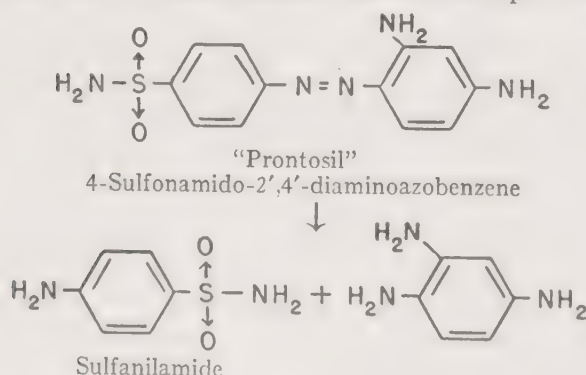
(acetylation) aided in the development of compounds that are acetylated to a lesser extent or whose acetylated derivatives are more soluble and therefore minimize kidney damage due to crystallization in the renal tubules. Likewise, studies on absorption of the sulfonamides from the intestine led to the introduction of the *N*⁴-acylated derivatives such as sulfasuxidine for the treatment of intestinal infections. The introduction of mandelic acid as a genito-urinary antiseptic followed the observation^{4,5} that it is excreted unchanged and if kept in an acid environment in the urine, possesses significant bactericidal activity.

SITE OF DETOXICATION

The chemical changes substances undergo in the body are believed to occur principally in the intestines, the liver and the kidneys, with the liver serving as the dominant organ. The role of the liver in detoxication has been supported with a wealth of data obtained from studies on hepatectomized animals. In this connection it should be kept in mind that great differences exist in the chemical changes a substance undergoes in different species of animals. As an example, the fowl excretes benzoic acid largely as ornithuric acid, while man excretes it principally as hippuric acid with only five to ten per cent excreted as the glucuronide. The dog, on the other hand, excretes approximately 75 per cent of the benzoic acid as the glucuronide. Phenylacetic acid has been found to be excreted by man largely in combination with glutamine; in the dog, cat, rabbit and monkey it is combined with glycine, and in the fowl it is combined with ornithine.

CHEMICAL CHANGES OF DRUGS IN THE GASTRO-INTESTINAL TRACT

Action of the Salivary Secretions. With the exception of troches, gargles and sublingual medication, most drugs administered orally have only superficial contact with the salivary secretions and are not altered significantly. The salivary secretions contain a number of enzymes, however, that are ca-



velopment of the sulfonamides as therapeutic agents. Later studies on the chemical changes of the sulfonamides in the body

pable of destroying certain drugs. Catalase, which catalyzes the decomposition of hydrogen peroxide, is present. Urease is present and it converts urea into ammonia and carbonic acid. Other amides, such as salicylamide, appear to be converted into the corresponding acid and ammonia. Ptyalin "salivary amylase" will, of course, hydrolyze starch and glycogen.

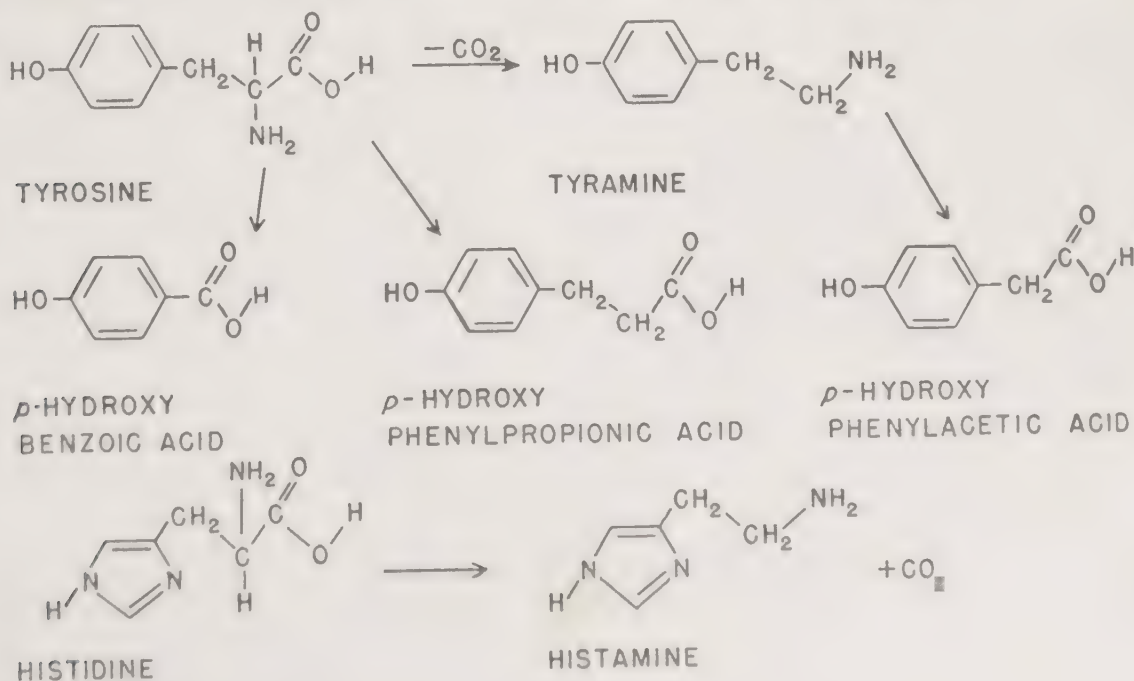
Action of the Gastric Secretions. The acid juices of the stomach contain the enzymes pepsin, rennin and lipase. Hydrochloric acid is present in approximately 0.5 per cent concentration and is thought to be responsible for most of the changes on drugs. The salts of biologically active amines probably are scarcely absorbed from the normal stomach. The salts of organic acids, however, will be converted to the free organic acids and may be absorbed from the stomach. The acid secretions of the stomach are thought to play an important role in facilitating the absorption of salts of weak acids, for example, the barbiturates (see Chap. 2). The ester drugs, atropine, syntropan, etc., normally will pass through the stomach unchanged.

Penicillin is quite unstable in the strong acid of the stomach, and penicillin products intended for oral administration usually are protected by an alkaline buffer in order to

minimize the decomposition. Insulin and other biologically active substances containing protein are more or less completely decomposed in the stomach. In addition to the decomposition and loss of activity a drug may undergo in the stomach, another consideration of considerable importance is the property of gastric irritation. Some agents such as the salicylates, ammonium chloride and others, tend to produce gastric irritation, and in such cases, are commonly administered with an enteric or a "time" coating.

Changes Occurring in the Intestines. The intestinal secretions, including bile and pancreatic juice, are responsible for a number of significant changes such as the hydrolysis of the aliphatic and aromatic esters, the glyceryl esters (fats), the anilids and related compounds.

All but the most resistant esters, i.e., atropine and other amino-alcohol esters, appear to be more or less completely hydrolyzed. Most absorption of foodstuffs and drugs takes place in the small intestine. In the large intestine occur putrefactive changes which are primarily due to bacterial activity. Some of the products formed by intestinal putrefactive changes are quite toxic, e.g., indole and skatole. Tyrosine and histidine will serve to illustrate the bacterial degradation of the amino acids.



DETOXICATION REACTIONS

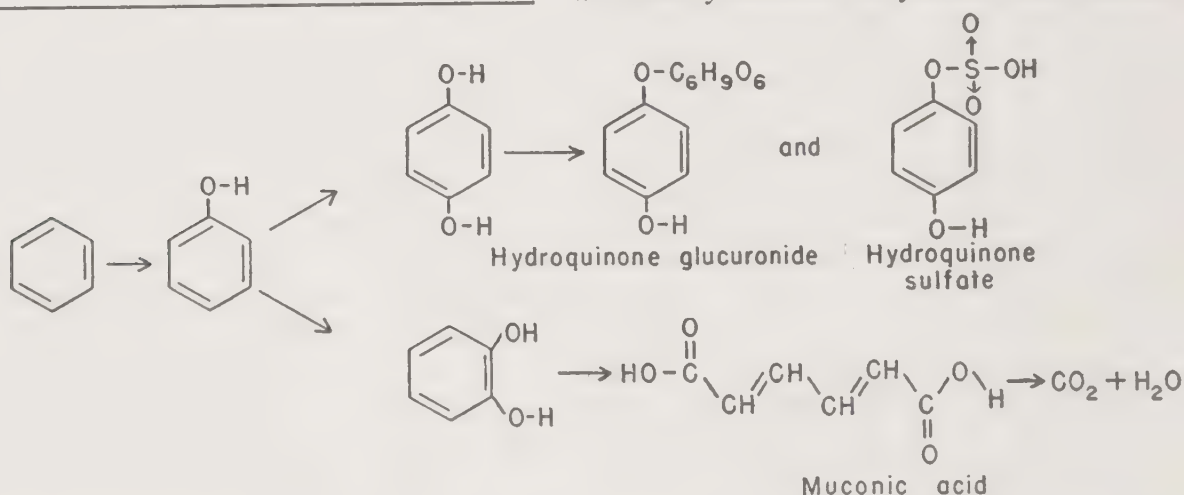
The types of chemical reactions involved in the changes drugs undergo in the body are principally: *oxidation, reduction, acetylation, hydrolysis, methylation and conjugation* with one of a number of metabolites, including *glycine, glutamine, cysteine, glucuronic acid*, etc. These reactions usually lead to more polar compounds that have greater water solubility and lower partition coefficients. Usually, the end products of metabolism (the compounds excreted) will be more acidic in character than the parent compound introduced.

An examination of the chemical changes various common classes of organic compounds undergo in the body will indicate

and in part oxidized to fatty acids. Some of the unsaturated hydrocarbons have been observed to undergo hydration in the body to form the corresponding alcohol, which may be conjugated with glucuronic acid.

The aromatic hydrocarbons, although resistant to oxidation, are oxidized in part. Benzene is partially oxidized to phenol, which in turn is oxidized in part to catechol, hydroquinone and muconic acid.

The aromatic hydrocarbons with short aliphatic side chains, for example, toluene, ethylbenzene, xylene and mesitylene, are oxidized to carboxylic acids or hydroxy carboxylic acids. Toluene and ethylbenzene are oxidized in part to benzoic acids. Ethylbenzene is also oxidized in part to phenylmethyl carbinol and mandelic acid. Xylene and mesitylene have only one of their methyl

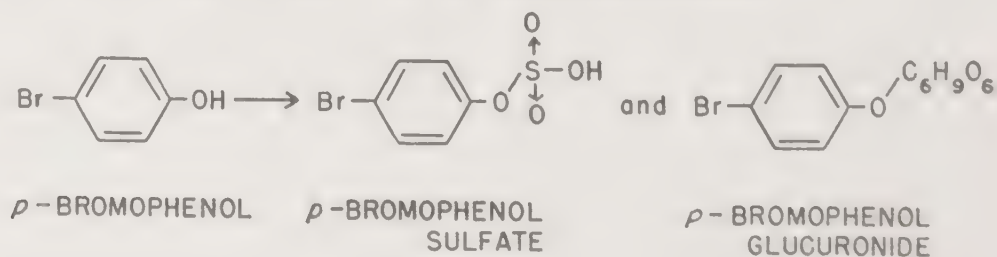


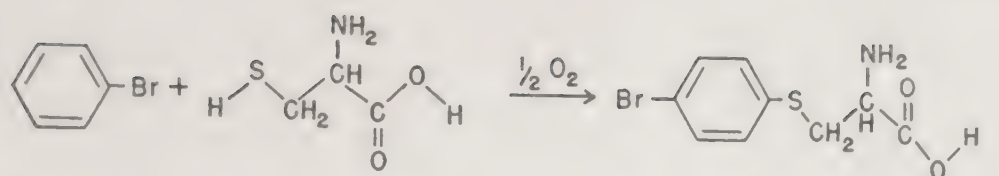
how the above reactions apply to the general process of detoxication.

HYDROCARBONS

The saturated aliphatic hydrocarbons of high molecular weight are normally considered to be poorly absorbed and to pass through the body unchanged. However, *n*-hexadecane has been shown⁶ to be absorbed by the rat, partially stored in the fat depots

groups oxidized. *n*-Propylbenzene is oxidized to benzoic acid. The acids formed from such hydrocarbons then are conjugated with glycine or glucuronic acid. The monohalogenated benzenes, e.g., bromobenzene and bromonaphthalene, are excreted in part as the halogenated phenylmercapturic acids and in part as the sulfates and glucuronides of the *p*-halogenated phenol.

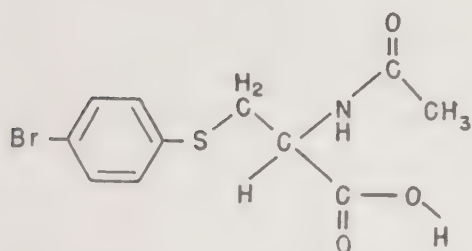




BROMOBENZENE

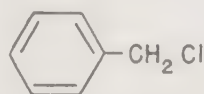
CYSTEINE

-BROMOPHENYL-CYSTEINE

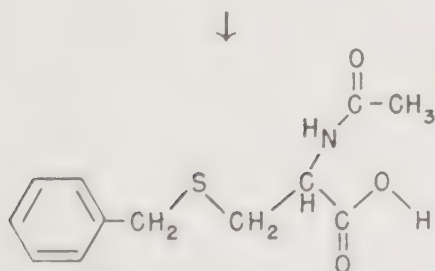


-BROMOPHENYLMERCAPTURIC ACID

Some of the monohalogenated benzenes are oxidized to the *p*-halogenated phenols and some of the corresponding ortho isomers also may be formed.⁷ The phenols then are excreted in combination with glucuronic acid or as ethereal sulfates (cf. phenols). Benzyl chloride has been shown to be partially excreted as *N*-acetyl-S-benzyl-cysteine (S-benzylmercapturic acid).⁸ This compound is of interest in that the sulfur is not attached directly to the aromatic ring, as it is in most mercapturic acids.

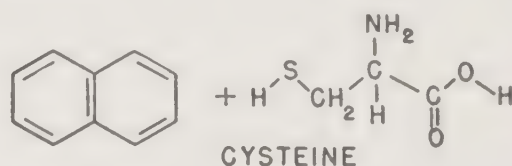


Benzyl Chloride

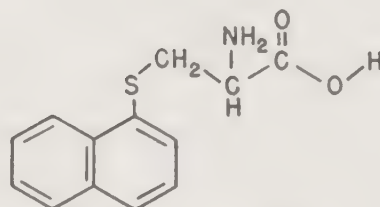
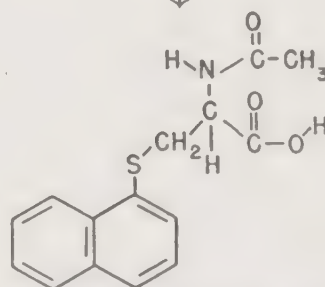


S-Benzylmercapturic Acid

Likewise, naphthalene is partially excreted as the α -naphthylmercapturic acid and in part as the sulfate and glucuronide of α -naphthol.

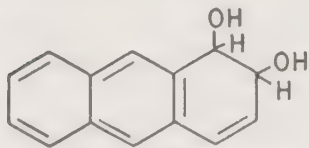


CYSTEINE

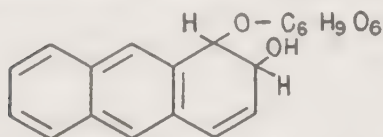
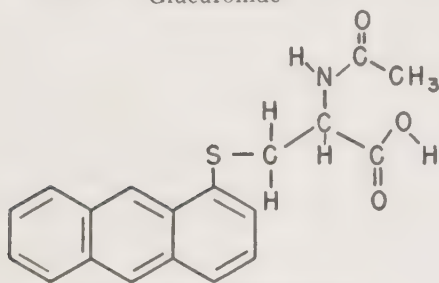

 α -Naphthyl-S-Cysteine

 α -Naphthylmercapturic Acid

Sulfhydryl-containing compounds, i.e., methionine and sodium thioglycollate, have been shown⁹ to protect the liver from damage by chloroform, which may be due to the formation of conjugated compounds similar to the mercapturic acids.

Anthracene is converted by the rat and the rabbit to 1,2-dihydroxy-1,2-dihydroanthracene, which then is excreted in combination with glucuronic acid. Some is also excreted as 1-anthrylmercapturic acid.

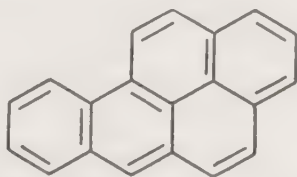


1,2-Dihydroxy-1,2-dihydro-anthracene

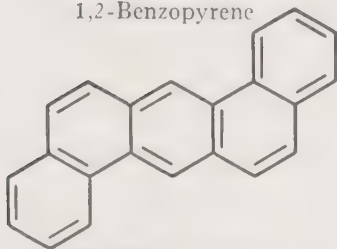
1,2-Dihydroxy-1,2-dihydro-anthracene
Glucuronide

1-Anthrylmercapturic Acid

The cancer-producing (carcinogenic) hydrocarbons such as benzopyrene, methylcholanthrene and dibenzanthracene are presumably resistant to chemical change in the body, but some oxidation and conjugation is known to occur.



1,2-Benzopyrene



1,2,5,6-Dibenzanthracene

1,2,5,6-Dibenzanthracene is partially oxidized to a dihydroxy compound which can conjugate with either sulfuric or glucuronic acid. It is likely that the oxidized and conjugated compounds are harmless. The conjugated biologically active steroids, by analogy, are usually relatively inactive¹⁰ as compared with the free steroids.

ALCOHOLS

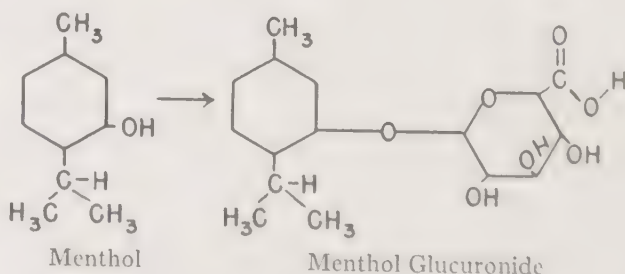
Many aliphatic compounds are oxidized in the body to carbon dioxide and water.

Ethyl alcohol and the primary and secondary alcohols of low molecular weight are, with exceptions, more or less completely oxidized. Tertiary alcohols and halogenated alcohols, e.g., tertiary butyl alcohol, tribromo-ethanol, trichloro-ethanol, etc., are resistant to oxidation and are excreted largely as the conjugates of glucuronic acid.

The glycols tend to be oxidized in the body to the corresponding mono or dicarboxylic acids. Those failing to undergo oxidation may conjugate in part with glucuronic acid or be excreted unchanged. Ethylene glycol oxidizes in the body to oxalic acid, which may cause a deposition of calcium oxalate in the renal tubules.¹¹ Propylene glycol is much less toxic than ethylene glycol and has been shown to be converted by the isolated cat liver to glycogen and to lactic acid.¹²

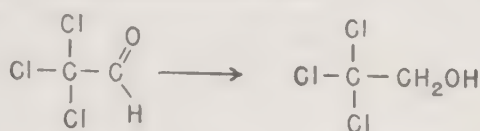
The primary aromatic alcohols are oxidized in part to benzoic or phenylacetic acid, depending on the number of carbons in the side chain. Benzyl alcohol, as an example, is oxidized to benzoic acid, β -phenylethyl alcohol to phenylacetic acid. γ -Phenylpropanol may undergo β -oxidation to benzoic acid, which will then conjugate with glycine (cf. acids).

The secondary aromatic alcohols, e.g., phenylmethyl carbinol, are more resistant to oxidation and are excreted in part as the conjugates of glucuronic acid.¹³ The tertiary aromatic alcohols, such as triphenylcarbinol, are excreted in part unchanged.¹⁴ The failure of triphenylcarbinol to conjugate may be due to steric hindrance. Hydroaromatic alcohols, such as menthol and borneol, are excreted largely as the glucuronides.



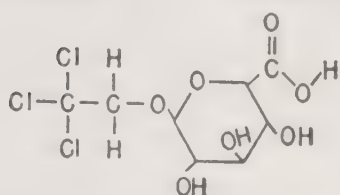
ALDEHYDES

Most of the simple aliphatic aldehydes are thought to be oxidized in the body to carbon dioxide and water. The halogenated aldehydes, e.g., chloral, and tertiary substituted aldehydes, are resistant to oxidation and may be reduced to the corresponding alcohols, which are then conjugated with glucuronic acid and excreted.



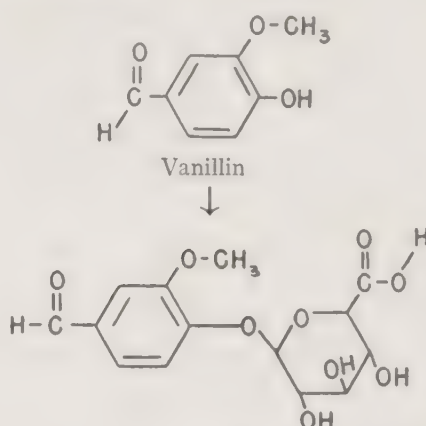
Chloral

Trichloro-ethanol


 Trichloro-ethanol Glucuronide
Urochloralic Acid

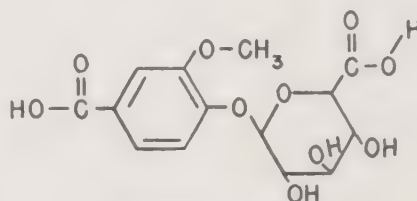
Most aromatic aldehydes are readily oxidized to the corresponding carboxylic acids. Benzaldehyde, administered orally or parenterally, is converted to benzoic acid. Cinnamic aldehyde is converted to cinnamic acid. Vanillin undergoes oxidation in the body to vanillic acid, which is then conjugated with glucuronic acid. The conjugation may precede the oxidation.¹⁵ This process may be illustrated with vanillin and glucuronic acid, keeping in mind, however, that

conjugation may also occur with sulfuric acid (cf. phenols).



Vanillin

Glucurovanillin

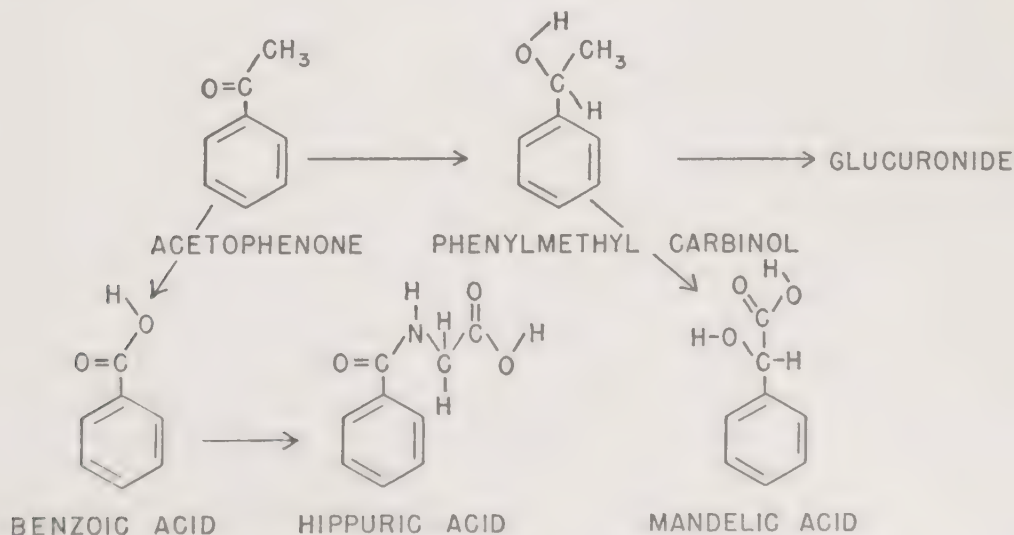


Glucurovanillic Acid

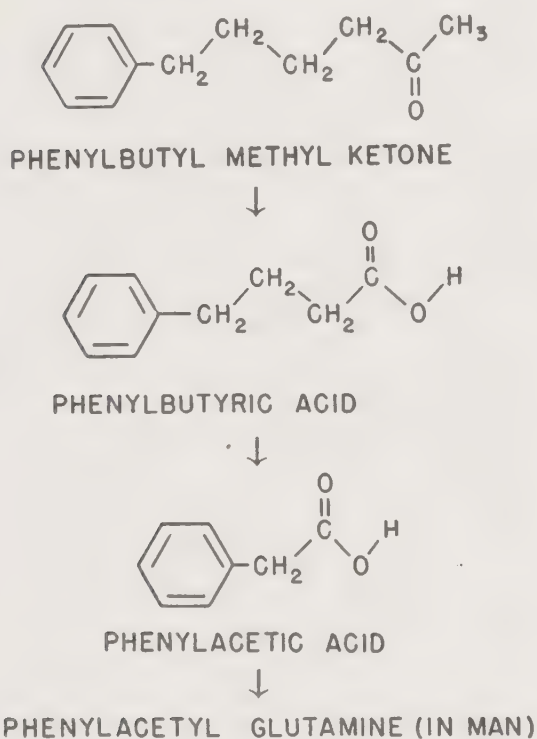
KETONES

With the exception of acetone, most of the aliphatic ketones appear to be largely oxidized in the organism. Acetone is somewhat resistant to oxidation and is partially excreted unchanged.

The mixed aromatic-aliphatic ketones are partially reduced to the secondary alcohols and in part oxidized to carboxylic acids.¹³ Acetophenone has been shown to undergo the following changes.

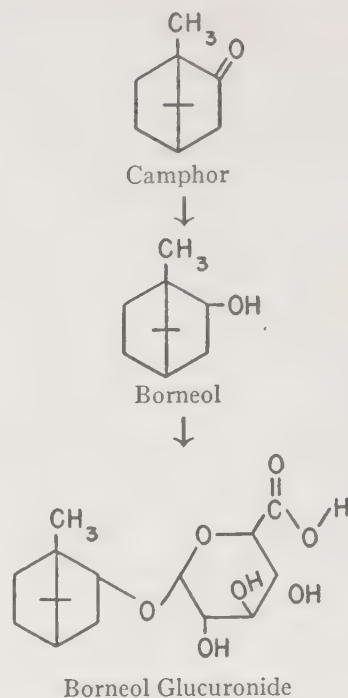


Benzyl methyl ketone is oxidized to benzoic acid; phenylethyl methyl ketone and phenylbutyl methyl ketone are oxidized to phenylacetic acid. This is in accord with the views of Dakin¹⁶ that "most aromatic methyl ketones primarily undergo oxidation in the body, so as to yield acids with two less carbons, except in the case of acetophenone in which the carbonyl group is directly attached to the nucleus." Phenylbutyl methyl ketone in man presumably successively forms γ -phenylbutyric acid, phenylacetic acid and phenylacetyl glutamine, which is excreted (cf. carboxylic acids).



Most of the quinones thus far studied appear to be resistant to oxidation in the body, and some are known to undergo reduction. 1,4-Benzoquinone (quinone) is reduced in part to hydroquinone, which is then conjugated with sulfuric and glucuronic acid. Vitamin K₃ (2-methyl-1,4-naphthoquinone) is oxidized in part to phthalic acid.¹⁷

Hydro-aromatic ketones resistant to oxidation, e.g., camphor, tend to be reduced to the secondary alcohol and conjugated in part with glucuronic acid.

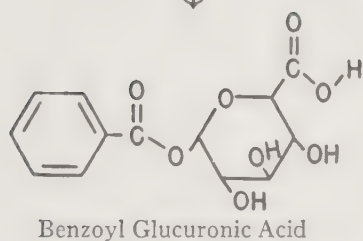
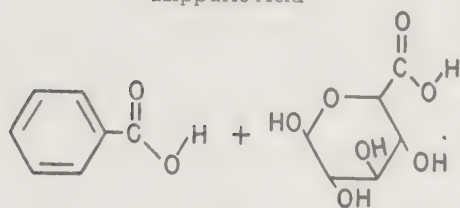
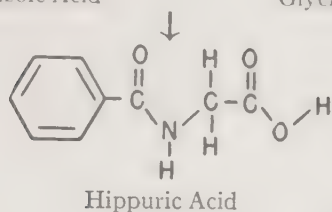
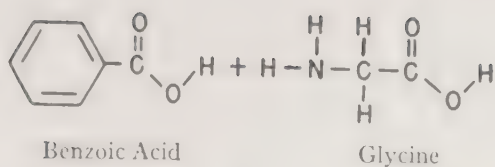


ACIDS

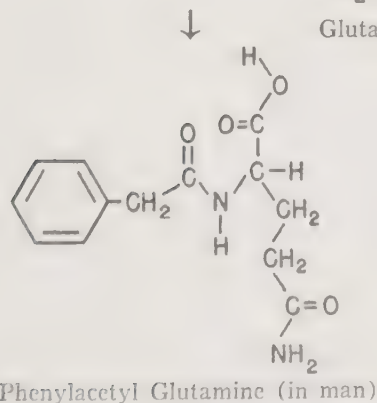
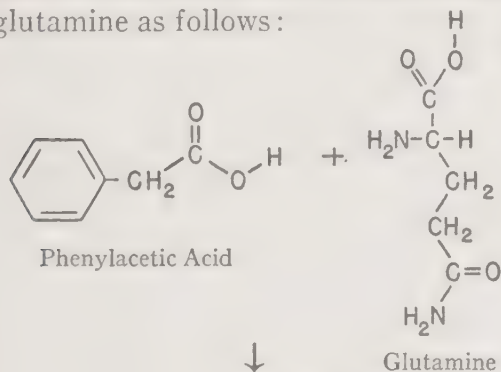
Carboxylic Acids. Even-numbered aliphatic carboxylic acids tend to be oxidized completely to carbon dioxide and water. The aliphatic amino acids likewise are oxidized to carbon dioxide, water and urea. Halogenated aliphatic acids, such as mono- and dichloroacetic acid, are resistant to oxidation and are partially excreted unchanged.

Aromatic carboxylic acids tend to conjugate in the body with one or more of several metabolites. The conjugates formed and excreted vary with the animal used. The metabolites commonly involved in the conjugation of the aromatic carboxylic acids are glucuronic acid, glycine, ornithine (in the fowl) and glutamine.

The excretion of benzoic acid has been studied carefully in a number of animals. There has been sustained interest in this acid because of its permitted use as a food preservative and because of its value as a test agent for liver function. All mammals thus far studied excrete benzoic acid in part as hippuric acid, and a number (man, sheep, pig, dog and rabbit) also excrete it as an ester of glucuronic acid. The following reactions, making use of benzoic and phenylacetic acids, will serve to illustrate the general detoxication reactions of the aromatic acids.

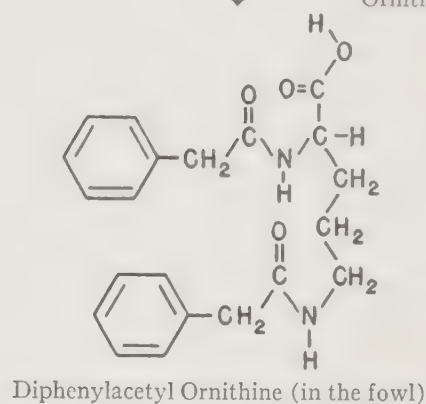
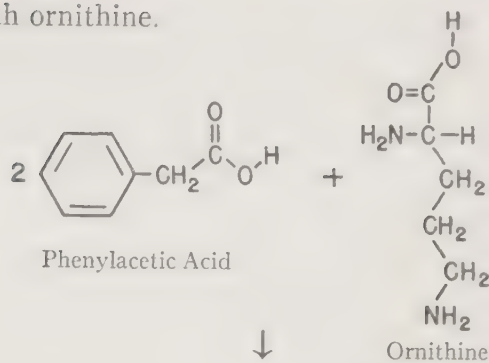


Diphenylacetic acid conjugates in part with glucuronic acid, as does benzoic acid.¹⁸ Phenylacetic acid does not conjugate with glycine in man, but is excreted as a conjugate of glutamine as follows:

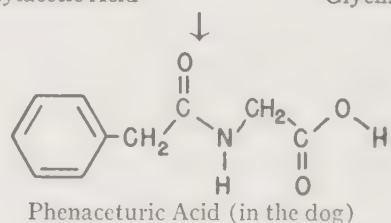
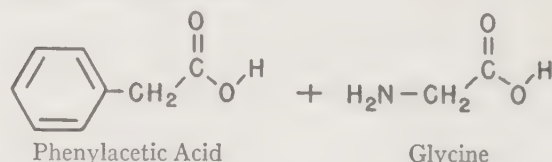


In the fowl, phenylacetic acid conjugates

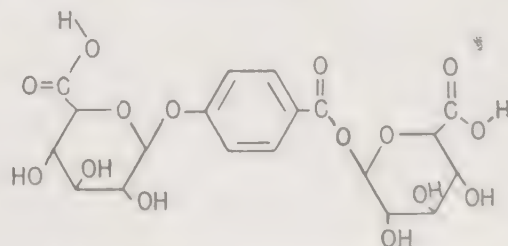
with ornithine.



In the dog, phenylacetic acid is converted to phenaceturic acid.



Aromatic carboxylic acids containing another functional group, i.e., -OH, -NH₂, etc., may be excreted in part as double conjugates. As an example, *p*-hydroxybenzoic acid has been shown¹⁹ to be excreted by the dog in part as the diglucuronide.

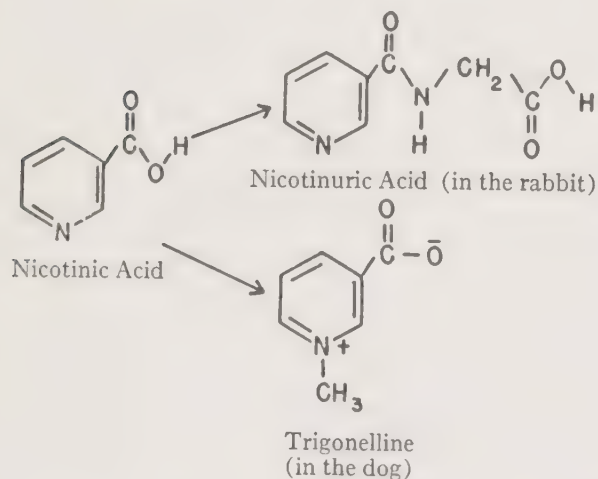


p-Hydroxybenzoic Acid Diglucuronide

A comparatively large amount of salicylic acid (approximately 55 per cent) is excreted by man as salicyluric acid; some (approximately 25 per cent) is excreted as the glucuronide.²⁰ Other metabolic products are yet to be discovered.

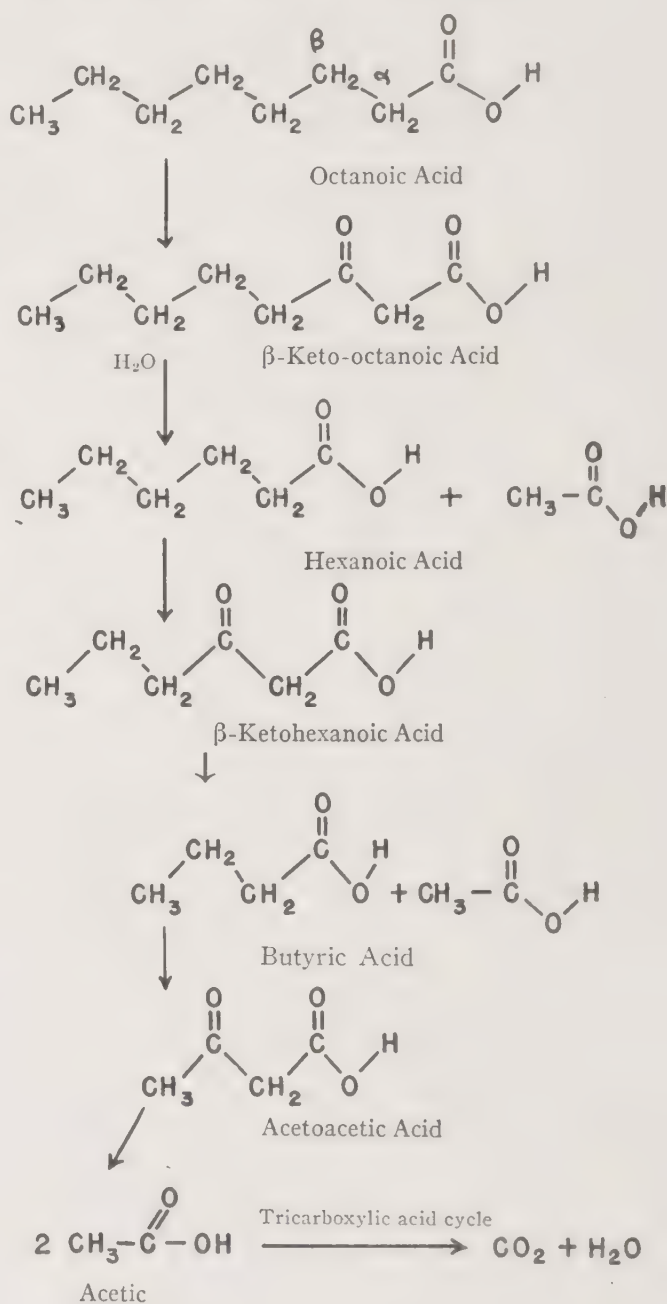
p-Aminobenzoic acid, which is now regarded as one of the group of B vitamins, is excreted by man largely as the acetyl derivative.²¹ Quick²² has shown that in dogs 60 to 70 per cent is excreted in conjugation with glucuronic acid. A number of the esters of *p*-aminobenzoic acid (ethyl, β -diethyl-amino-ethyl, etc.,) are employed as local anesthetics. In the body, the esters are hydrolyzed rapidly; this is followed by the oxidation of the alcohols or amino-alcohols and the acetylation of the *p*-aminobenzoic acid. This is shown for butyl aminobenzoate in the equation at the top of page 39.

Nicotinic acid is partially excreted by the rabbit as nicotinuric acid, but in the dog it is excreted in part as trigonelline²³ (cf. methylation, under amino compounds).

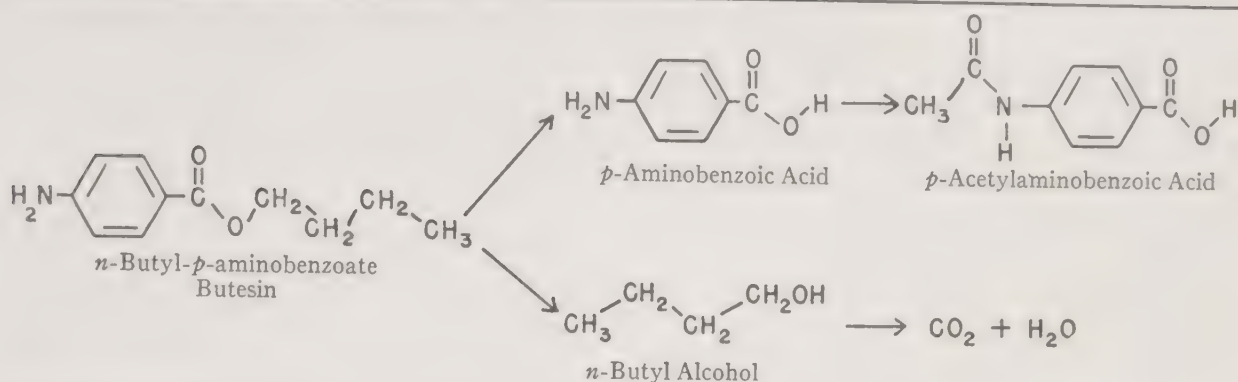


β -Oxidation of Carboxylic Acids. Knoop²⁴ was first to observe that the ω -phenyl substituted acids undergo β -oxidation leading to benzoic or phenylacetic acid, depending on the number of carbons in the side chain. Acids having an even number of carbons in the side chain oxidize to phenylacetic acid. Those with an odd number oxidize to benzoic acid. The acid formed then conjugates with glycine or glucuronic acid before excretion.

Knoop's theory proposes the following scheme to explain the degradation of the normal fatty acids. The process consists of β -oxidation followed by hydrolysis.

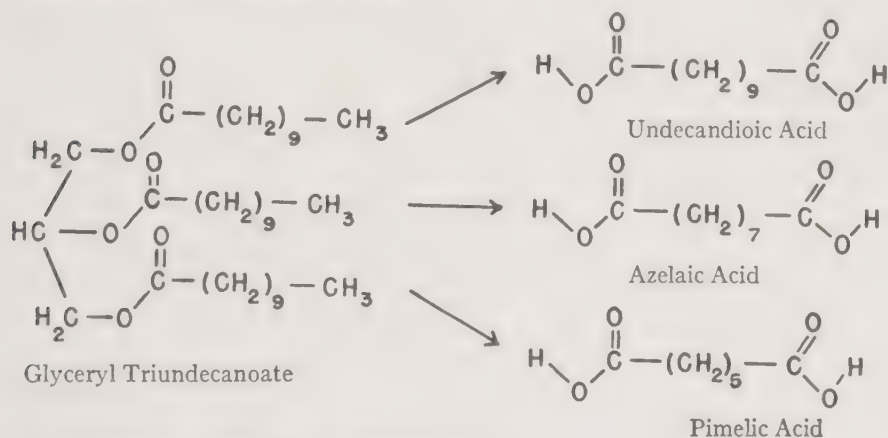


In addition to β -oxidation, multiple alternate oxidation²⁵ (simultaneous β -oxidation)²⁶ may occur, and oxidation of the terminal carbon (methyl group)—"omega-oxidation"²⁷ of fatty acids is also known to occur. ω -Oxidation leads to the formation of dicarboxylic acids. The feeding of the triglyceride of undecanoic (C_{11}) acid, as an example, is found to form three dicarboxylic acids: undecandioic (C_{11}), azelaic (C_9) and pimelic



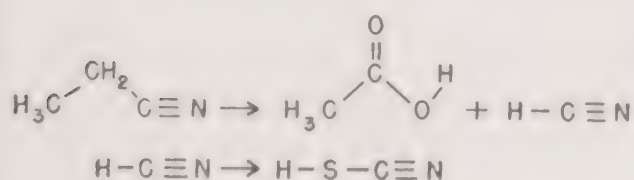
(C₇). Likewise, the feeding of undecandioic acid to dogs shows that part of the compound is excreted unchanged and part is oxidized to azelaic and pimelic acids.

In the body, the formation of thiocyanic acid from hydrocyanic acid is brought about by the enzyme rhodanese,²⁸ which is widely



Sulfonic Acids. The aromatic compounds containing a sulfonic acid group attached to the nucleus are, in general, considered to be excreted unchanged. Compounds of this type, such as benzene sulfonic acid, are of course strong acids and will usually have low partition coefficients. Likewise, *n*-octan-sulfonic acid when fed to the dog, has been observed to be excreted unchanged for the most part.

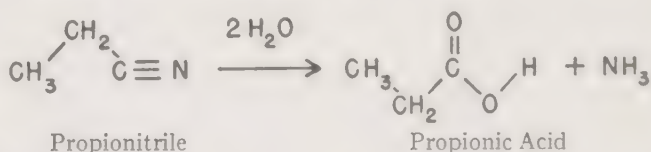
Nitriles. The aliphatic nitriles are partially broken down in the body to hydrocyanic acid, which is then excreted as thiocyanate. According to Williams, the reaction involves an oxidative degradation which may be shown for propionitrile as follows:



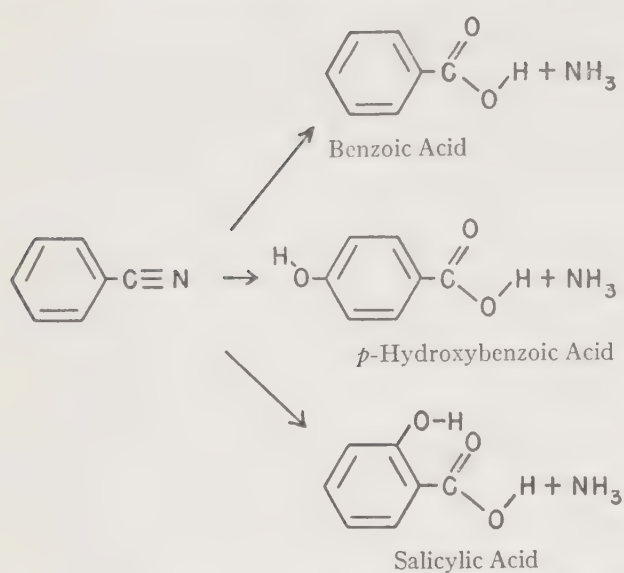
distributed in animal tissue. Lang²⁸ has shown that thiocyanic acid is formed from hydrocyanic acid and sodium thiosulfate in vitro and that the reaction does not require oxygen:



In addition to splitting off HCN, the aliphatic nitriles undergo some hydrolysis to the corresponding acids (Williams).



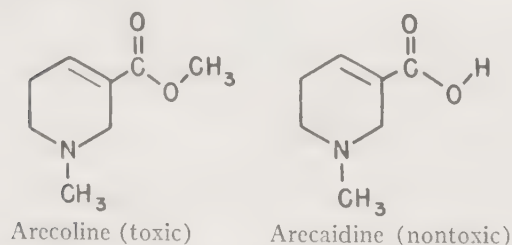
The aromatic nitriles appear to undergo hydrolysis with or without oxidation. Based on the work of Giacosa²⁹ and Baumann,³⁰ Williams suggests that benzonitrile undergoes in part the following changes in the body.



It is not known whether oxidation occurs before or after the hydrolysis of the nitrile. The benzoic, *p*-hydroxybenzoic and salicylic acid formed will then conjugate with glycine and glucuronic acid (cf. carboxylic acids).

ESTERS

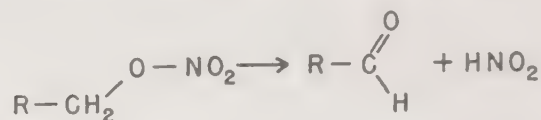
The biologically active esters, in general, lose their pharmacologic activity and most of their toxicity when hydrolyzed. This is the most likely method for the detoxication of the large number of ester drugs in use. The process may be expected to apply to most of the commonly employed ester drugs, e.g., local anesthetics, antispasmodics, parasympathomimetics, etc. Arecoline, an alkaloid ester occurring in the seeds of *Areca catechu*, will serve to illustrate the influence of hydrolysis on the toxicity of biologically active esters.



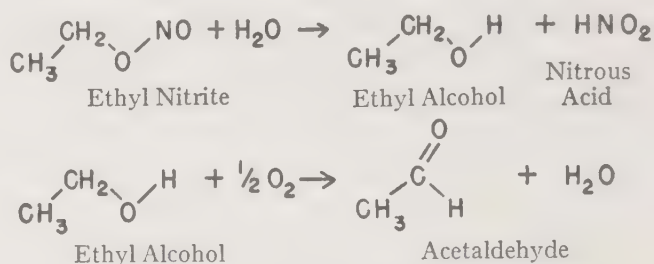
The nitrite and nitrate esters of the aliphatic alcohols, e.g., glyceryl trinitrate, erythrityl tetranitrate, amyl nitrite, etc., are detoxified by hydrolysis.

Whitmore³¹ suggests that the nitrate esters undergo an intramolecular oxidation in

accordance with the following reaction:



The nitrite esters, by a different mechanism (hydrolysis followed by oxidation), may give the same products in the body as the nitrate esters. This may be shown for ethyl nitrite as follows.



The aldehyde will undergo further oxidation to give carbon dioxide and water.

Krantz *et al.*³² have published evidence to show that the action of the nitrate esters may be due to the unhydrolyzed molecule and not to products of hydrolysis. They find in a series of nitrates of glycollic acid and its esters that the observed activity parallels the partition coefficients. The following compounds were studied (see Table 7).

TABLE 7. ACTIVITY AND PARTITION COEFFICIENTS OF DERIVATIVES OF GLYCOLLIC ACID*

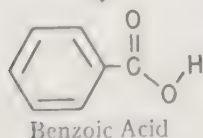
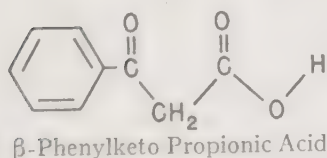
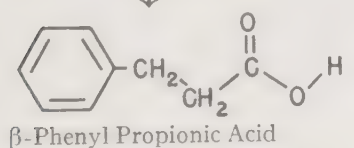
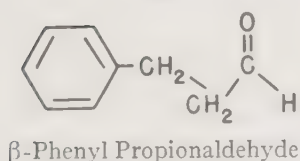
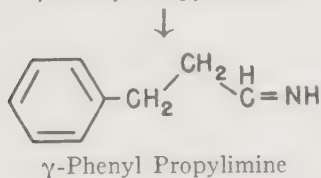
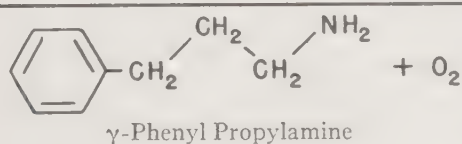
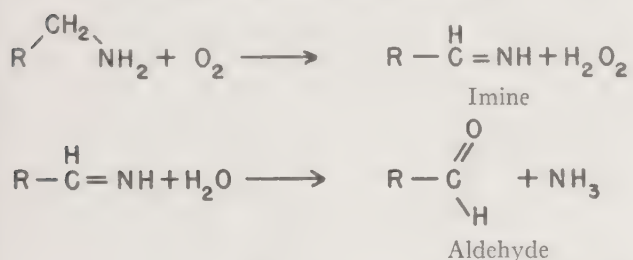
COMPOUND	EFFECTIVE DEPRESSOR (MOLAR CONCENTRATION)	PARTITION COEFFICIENT (OIL/WATER)
Sodium glycollate nitrate..	0.10	0.9
Ethyl glycollate nitrate....	0.013	17.0
<i>n</i> -Propyl glycollate nitrate..	0.008	24.0
<i>n</i> -Butyl glycollate nitrate..	0.003	108.0
<i>n</i> -Heptyl glycollate nitrate..	0.001	142.0

* After Krantz, J. C., Jr., Carr, C. J., Forman, S., and Cone, N.: J. Pharmacol. & Exper. Therap. 70:323, 1940.

AMINO COMPOUNDS

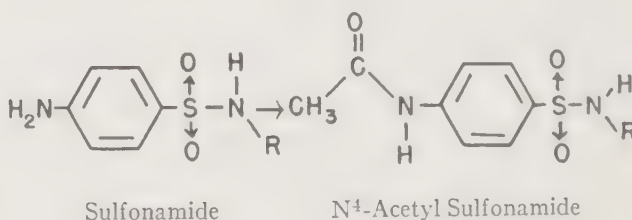
Primary aliphatic amines are for the most part oxidized to carbon dioxide, water and urea. Those compounds having the primary amino group attached to a secondary carbon, e.g., ephedrine, amphetamine, etc., are more

resistant to oxidative deamination than the normal amines and are excreted partially unchanged. The amine oxidase responsible for deamination is present in low concentration in many animal tissues and is inhibited by those amines having a methyl group on the alpha carbon. Biologically active amines, i.e., amphetamine, Paredrine, Tuamine, ephedrine, etc., having an α -methyl group will therefore tend to give a longer duration of action than the normal primary amines. The action of amine oxidase on primary amines may be shown as follows:



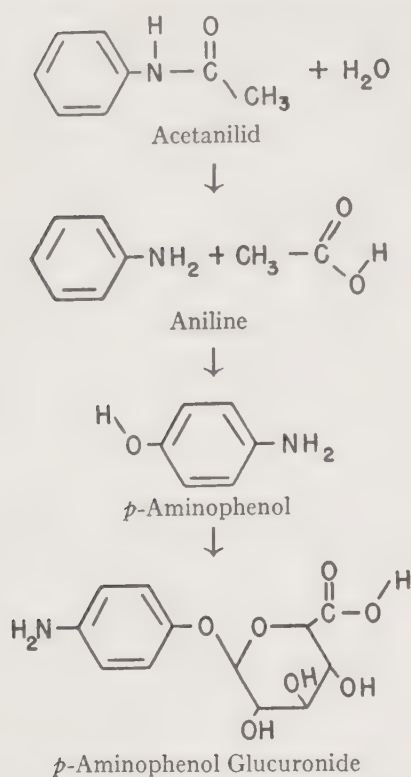
The aromatic alkylamines, i.e., benzylamine and β -phenylethylamine, have been shown to be oxidized to benzoic and phenylacetic acid. The oxidation undoubtedly involves the intermediate formation of the corresponding aldehydes. γ -Phenyl propylamine has also been shown to be oxidized to benzoic acid, and this may be explained in the same manner, the final step involving β -oxidation (cf. carboxylic acids). (See last equation in column 1 for the steps in the oxidation of γ -phenyl propylamine to benzoic acid.)

A relatively large number of aromatic amines have been shown to undergo acetylation in the body. *p*-Aminobenzoic acid and the sulfonamides may be cited as examples of compounds that are acetylated. The extent of the acetylation varies not only with the compound but also with the animal used. Man excretes sulfanilamide and other sulfonamides in part as the *N*⁴-acetyl derivative.



In addition to the acetylation of aromatic amino groups, acetylation may also occur on the α -amino group of some of the amino acids. As an example, *S*-benzyl-cysteine has been shown to be acetylated to the benzylmercapturic acid. It is possible that the acetylation process may be the last step in the formation of the mercapturic acids (cf. hydrocarbons).

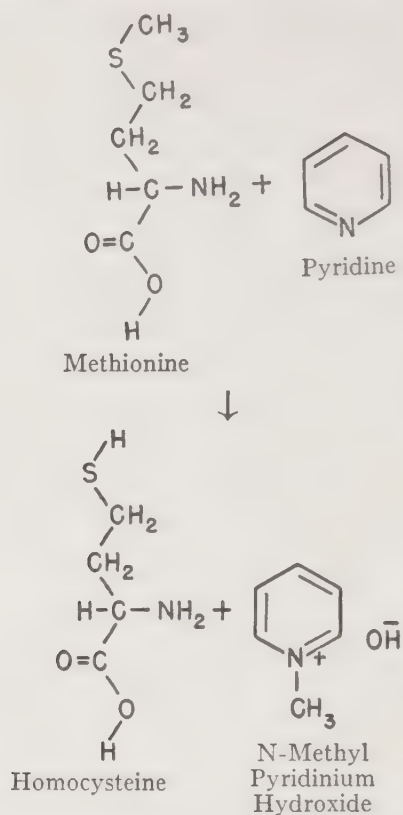
Some of the aromatic amino compounds undergo oxidation in the body to phenolic derivatives. Greenberg and Lester³³ have shown that from 70 to 90 per cent of the acetanilid in man is converted to *p*-aminophenol and is excreted in conjugation with sulfuric and glucuronic acid. This may be shown as follows:



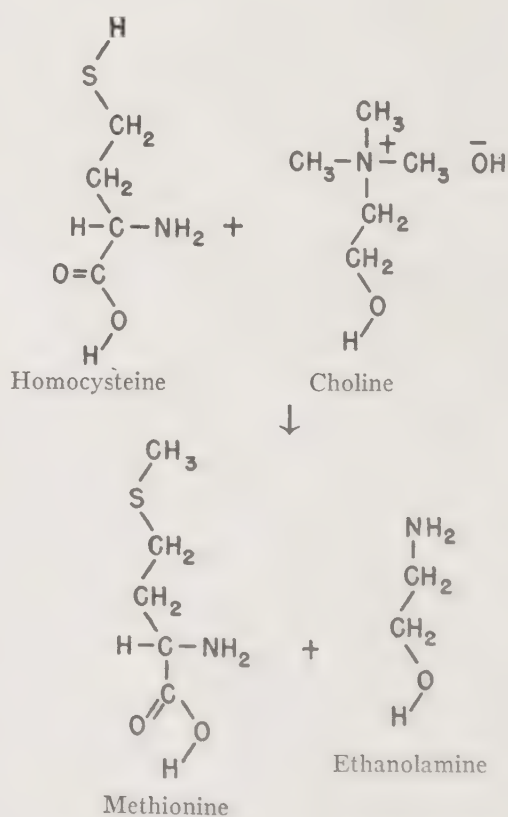
Some methylated amino compounds undergo demethylation. As an example, dimethylaniline in the dog has been shown to be completely demethylated and oxidized to *o*-aminophenol,³⁴ which is excreted in conjugation with sulfuric and glucuronic acid. In the rabbit, however, it is converted to *p*-monomethylaminophenol and excreted as the glucuronide.³⁵ Likewise, the methylated xanthines, e.g., caffeine, theobromine, etc., undergo demethylation in the body.

A number of amines are known to undergo methylation in the body, and the methylation process is recognized as one of the detoxication methods. To illustrate, pyridine is excreted as a salt of N-methyl pyridinium hydroxide, quinoline as a salt of N-methyl quinolinium hydroxide and nicotinic acid is excreted in part as trigonelline.

The essential amino acid methionine, in combination with choline, has been shown to be the principal biologic methylating agent, and the mechanism of this detoxication process may be illustrated by showing the conversion of the relatively toxic pyridine into pyridinium hydroxide, which forms a relatively nontoxic salt.

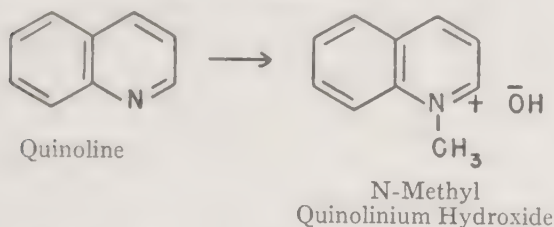


The homocysteine then is converted to methionine by choline as follows:



In the same manner, nicotinic acid is

methylated in part to trigonelline (cf. carboxylic acids), and quinoline is methylated to its *N*-methyl derivative.

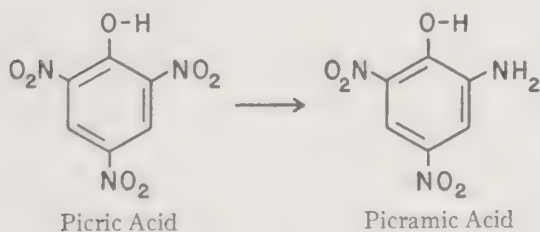


The fact that pyridine, which is relatively toxic, and nicotinic acid, which is an essential metabolite (vitamin), are both methylated suggests that the "detoxication process" may not always serve a useful purpose.

NITRO COMPOUNDS

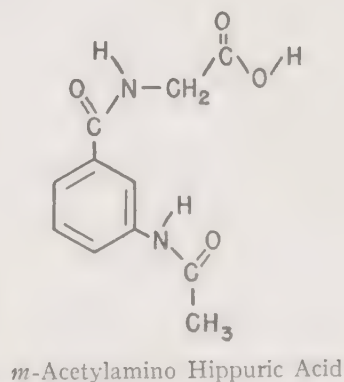
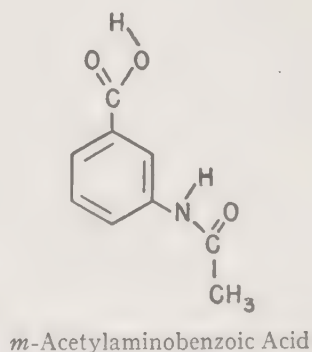
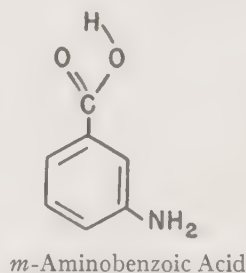
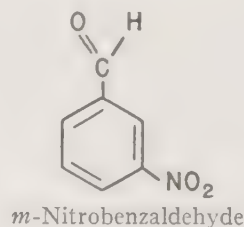
As a rule, the aromatic nitro compounds are reduced to the amino derivative and then acetylated. Nitrobenzene undergoes both oxidation and reduction in the body to form some *p*-aminophenol, which is then conjugated and excreted in part as the glucuronide. In general, the nitrophenols tend to be reduced to the corresponding aminophenols, which may then conjugate with glucuronic acid.

Aromatic compounds containing more than one nitro group, e.g., dinitrophenol, picric acid, etc., have only one of the nitro groups reduced. The formation of picramic acid from picric acid illustrates this reduction.



Aromatic nitro compounds, having substituents easily oxidized, may be expected to undergo both oxidation and reduction. Thus, the mononitrobenzaldehydes are oxidized to the corresponding nitrobenzoic acids. The meta and para isomers are then conjugated in part with glycine and excreted as hippurates. It has also been shown that the *m*-nitrobenzaldehyde is oxidized and re-

duced to *m*-aminobenzoic acid, which is then excreted in part as the acetyl derivative.



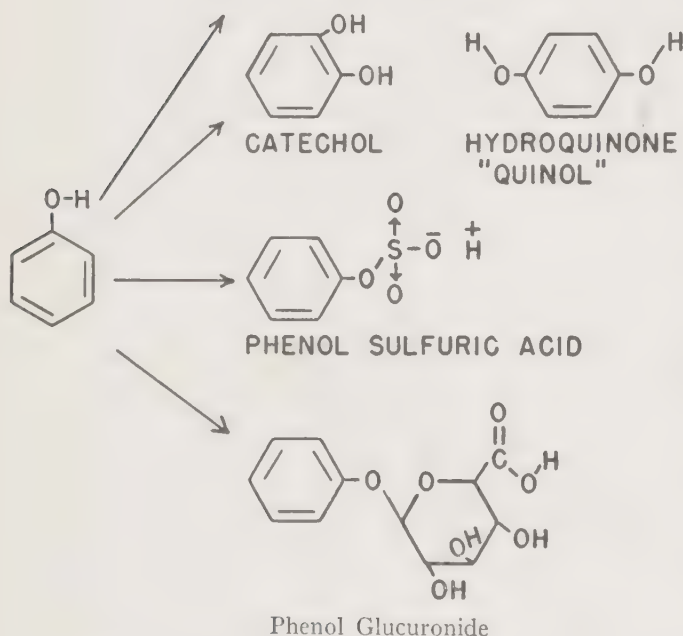
The mononitrophenylacetic acids are excreted by man partially unchanged.

PHENOLS

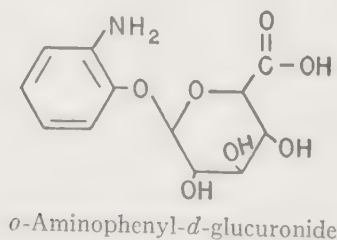
Three types of chemical changes are associated with the phenols in the organism, namely: oxidation, conjugation with glucuronic acid and conjugation with sulfates to form the sulfuric acid esters. Some phenolic compounds are excreted partially unchanged.

Phenol will serve to illustrate the types of chemical change that are common to the phenols.

EXCRETED UNCHANGED



The sulfates and glucuronides normally are excreted as the sodium salts. The methyl-substituted phenols are oxidized in part to the corresponding carboxylic acid. *p*-Cresol, as an example, is partially oxidized to *p*-hydroxybenzoic acid, which can then conjugate with glucuronic acid. The *o*- and *m*-aminophenols³⁶ are reported to be excreted entirely in conjugation with sulfuric and glucuronic acids.



p-Aminophenol, although it conjugates in the same manner as the ortho and meta isomers, is excreted partially unchanged (cf. acetanilid, under amino compounds). It is of interest to note that the *o*- and *p*-aminophenyl glucuronides are capable of forming methemoglobin in vitro. This property is not shown by the *m*-aminophenol or its conjugate with glucuronic acid.

Methyl salicylate and salicylamide are excreted partially as sulfuric acid esters.

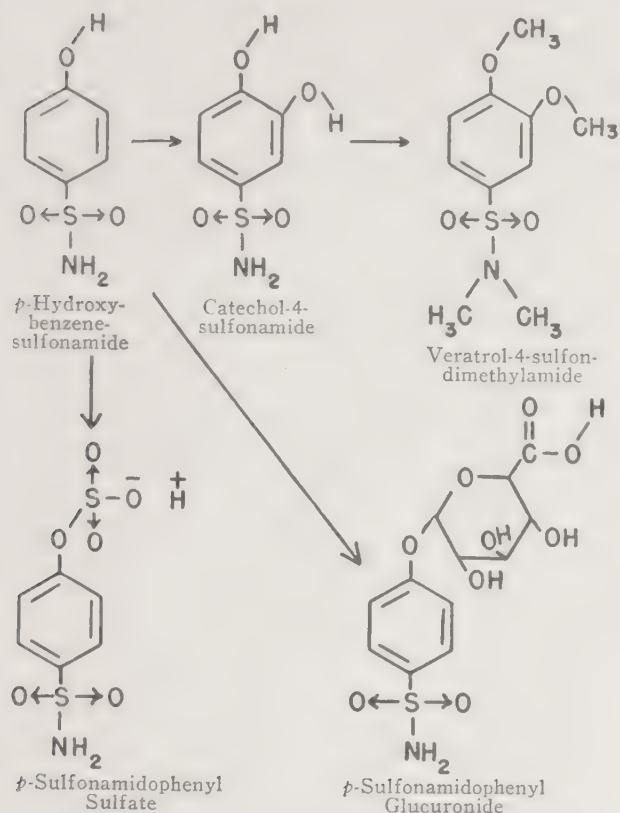
A study³⁷ of the excretion of sulfates by the rabbit following the administration of phenol and mono-substituted phenols indicates that the substitution of an acidic group in the ortho position to the hydroxyl in phenol, i.e., salicylic acid, decreases the tendency to conjugate with sulfuric acid. The substitution of a basic group in the ortho position, i.e., *o*-aminophenol, increases the tendency for sulfate conjugation. A neutral group in the ortho position, i.e., *o*-chlorophenol, does not alter the conjugation. The corresponding *m*-mono-substituted phenols behave qualitatively in the same manner as the ortho-derivatives. Substitution of a carboxyl group (*p*-hydroxybenzoic acid) in the para position greatly decreases sulfate conjugation, but the *p*-CONH₂ group increases sulfate conjugation.

The administration of *p*-hydroxybenzene sulfonamide to rabbits yields data which indicate that approximately 80 per cent of the compound is excreted as the sulfate or glucuronide.³⁸ A portion of the sulfonamide is oxidized to catechol-4-sulfonamide, which, in turn, is methylated to veratrole-4-sulfon-dimethylamide. (See equations in top left-hand column of page 45 for these reactions.)

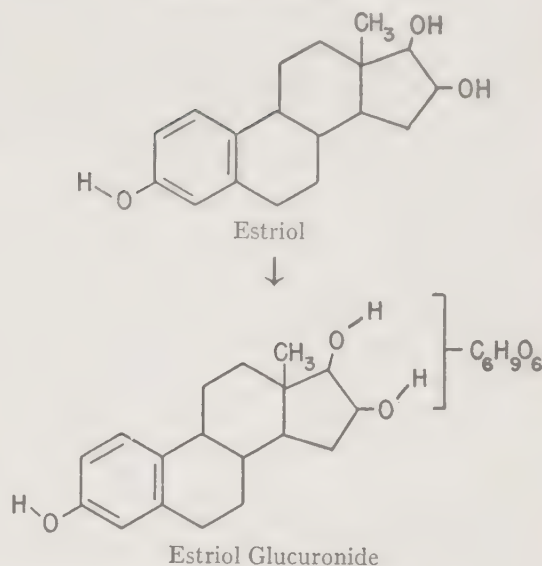
Phenolphthalein is excreted by man partially in combination with glucuronic acid. It is also conjugated in part with sulfuric acid. Thymol, carvacrol, β -naphthol and other phenols undergo the same type of conjugation.

SEX HORMONES

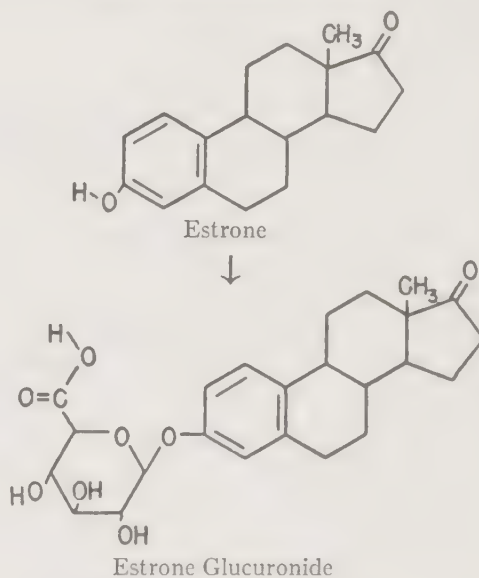
The fact that the estrogenic hormones are carcinogenic when administered to animals



Conjugation of Estriol



Conjugation of Estrone



hereditarily sensitive to the development of mammary cancer has stimulated interest in the chemical changes such compounds undergo in the body. It was recognized early that the estrogenic substances in pregnancy urine were present in a combined form which is for the most part inactive. It is now known that substances such as estriol, estrone and other estrogenic substances are excreted in part as the glucuronides^{10, 39, 40} and in part as the sulfates.⁴¹ This type of conjugation is, of course, to be expected of alcohols and phenols resistant to oxidation, and it conforms to the behavior of some of the simpler alcohols and phenols already mentioned. The sex hormones usually contain either phenolic or alcoholic hydroxyl groups or both. Estriol contains both types of hydroxyl groups, but in its conjugated form with glucuronic acid, the phenolic hydroxyl (C₃) is free. The glucuronic acid is attached to the alcoholic hydroxyl on C₁₆ or C₁₇. In estrone, the glucuronic acid is attached to the C₃ phenolic hydroxyl.

As compared to the free steroids, the conjugates (sulfates and glucuronides) are highly soluble in water or polar solvents and comparatively insoluble in ether, benzene or other nonpolar solvents.

Evidence has been presented⁴² to show that extensive liver damage almost completely eliminates conjugation of the natural estrogens and that the human male metabolizes therapeutic doses of the natural estrogens. The compounds formed and the amount of the estrogen excreted are influenced by the vehicle in which the estrogen is administered, by the route of administra-

tion and by the nature of the chemical conjugation.

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4

Aliphatic and Cycloparaffin Hydrocarbons

ALKANES (SATURATED HYDROCARBONS)
ALKENES (OLEFINS, ALKYLENES, UNSATURATED ALIPHATIC HYDROCARBONS)

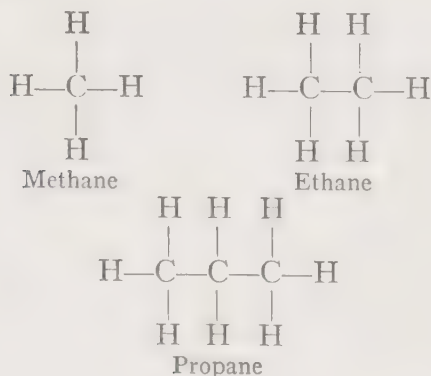
ALKINES (ACETYLENES, ETHINES)
DIENES OR DIOLEFINS
CYCLOPARAFFINS (POLYMETHYLENES, NAPHTHENES, ALICYCLIC HYDROCARBONS)

ALKANES (SATURATED HYDROCARBONS)

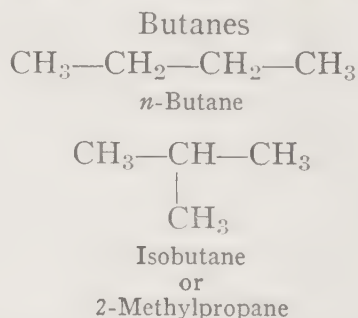
Alkanes or paraffin hydrocarbons are a very stable group of compounds of carbon and hydrogen comprising methane, CH_4 , and its homologues. Their generic formula is $\text{C}_n\text{H}_{2n+2}$.

As the series increases in carbon chain length, the physical properties of normal alkanes show a gradation from gases, CH_4 to C_5H_{12} , to liquids up to about $\text{C}_{16}\text{H}_{34}$, then low-melting solids up to about $\text{C}_{23}\text{H}_{48}$ and rigid solids up to $\text{C}_{94}\text{H}_{190}$, the longest alkane synthesized.

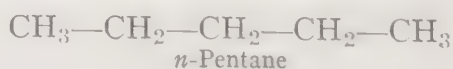
For the first three members of the series, only normal, straight chain compounds are possible:

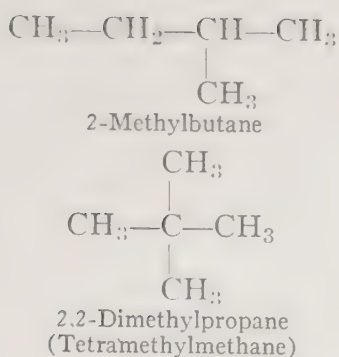


Beyond this, isomeric forms, having the same empirical formula but different chemical and physical properties, are possible:



The name 2-methylpropane is preferred for the isomeric or branched chain form of butane. It is representative of the Geneva system of nomenclature, in which the carbon atoms are arranged in the longest chain possible and numbered consecutively from one end of the chain. The substituents then are located by indicating the number of the carbon atom to which they are attached, the lowest possible number being used as a prefix. Thus, in the three isomeric pentanes, the second member is called 2-methylbutane and not 3-methylbutane.





The prefix methyl, applied to the CH_3 group, is typical of the name applied to a radical derived from an alkane with one hydrogen atom removed, the suffix *yl* replacing *ane*: methane, methyl (CH_3); butane, butyl (C_4H_9); alkane, alkyl, the latter being generic for saturated radicals and designated by the symbol R.

PREPARATION

Alkane hydrocarbons have been found in small amount in vegetable sources:¹ *n*-heptane, C_7H_{16} , in some species of pine; eicosane, $\text{C}_{20}\text{H}_{42}$, in spinach and in rose buds; nonacosane, $\text{C}_{29}\text{H}_{60}$, in pears and cabbages, and hentriacontane, $\text{C}_{31}\text{H}_{64}$, in beeswax.

Commercial sources of the alkanes include natural gas and petroleum. The lower members, up to C_5H_{12} , are found in gas wells in the United States; the gases are piped or compressed and used directly as fuel sources, or more recently, synthesized into liquid fuels. Petroleum is, however, the major source of hydrocarbons. The composition of crude petroleum is indeed complex. It is made up of hundreds of different compounds. In addition to small percentages of nitrogen, sulfur and oxygen-bearing compounds present in some petroleums, the hydrocarbon content may include paraffins, straight and branched-chain types; traces of olefins and other unsaturated aliphatic hydrocarbons; naphthenes or cycloparaffins of the generic formula C_nH_{2n} , having five or six carbon atoms in the ring, with paraffinic or naphthenic side chains, and aromatic or benzene hydrocarbons of generic formula $\text{C}_n\text{H}_{2n-6}$. Higher molecular weight hydrocarbons include cycloparaffin-aromatic

structures with paraffinic side chains. The composition varies with the source. Pennsylvania oils have a high content of paraffinic hydrocarbons with a residue of solid paraffins. Midcontinent oils have a higher naphthenic and aromatic hydrocarbon content, and Russian oils consist mostly of naphthenic hydrocarbons.

The commercial isolation of hydrocarbon fractions consists of a series of distillations of crude petroleum and subsequent washings and purifications. The lowest liquid fraction, boiling range under 20°C ., consists mainly of butane and pentane, and was used formerly as a topical refrigerant type anesthetic. The next fraction, petroleum ether, boiling range 35 to 80°C ., is chiefly pentane (C_5H_{12}) and hexane (C_6H_{14}).

Gasoline, because of its extensive demand, may be collected over a wide boiling range, 40 to 215°C . Gasoline embraces a wide range of hydrocarbons, saturated and unsaturated, branched and straight chain, up to $\text{C}_{12}\text{H}_{26}$. Gasolines containing highly branched chain hydrocarbons show little tendency to "knock" or explode violently under compression in a combustion cylinder. This quality of gasoline is expressed in terms of its octane number, the isomeric octane 2,2,4-trimethylpentane having been arbitrarily set as the standard in measuring antiknock performance. A 100-octane rating means that a gasoline corresponds to the knocking characteristics of the pure isomeric octane, signifying high antiknock properties. The maximum "knock" is obtained from heptane (C_7H_{16}). A 70-octane gasoline has the same "knock" characteristics as a mixture of 70 per cent iso-octane and 30 per cent *n*-heptane.

Kerosene is the hydrocarbon fraction collected at from 175 to 275°C . and comprises $\text{C}_{12}\text{H}_{26}$ to $\text{C}_{16}\text{H}_{34}$ compounds. Gas oil, collected above 275°C ., includes light household burning oils, heavier furnace oils and power generating oils such as diesel oil. They are graded on the basis of volatility, viscosity and ignition characteristics.

For some types of petroleum, further distillation under steam superheating yields the heavy distillate, from which paraffin waxes, lubricating oils and some light and medium viscosity mineral oils are obtained. For Pennsylvania and midcontinent oils, the residue, after fuel oil distillation, is utilized as a source of lubricating and mineral oils, paraffin wax and petrolatum. This residue is vacuum distilled under steam injection at about 315° C. yielding "wax distillate" and a nonvolatile residue. The former is chilled (—3° C.) under 300 pounds pressure and filter-pressed, effecting a partial separation of oil and wax. The waxy material is then "sweated" or warmed in shallow pans or dissolved in benzine or other solvents and chilled, permitting a further separation of oil from wax. The latter is then filtered hot through charcoal and cast into blocks, resulting in the familiar crystalline paraffin utilized for paper coating, candles and pharmaceutical ointment bases. The oil filtrate from the wax presses is steam distilled, and the residual oil is purified by filtration through granular bleaching clays, yielding high grade lubricating stock oils and heavy mineral oil.

The nonvolatile residue left after the vacuum distillation of the "wax distillate" is diluted with naphtha, filtered, chilled and centrifuged, yielding a soft amorphous wax which represents crude petrolatum. This is refined to remove unsaturated hydrocarbons either by sulfuric acid or by filtration through boneblack or fuller's earth.

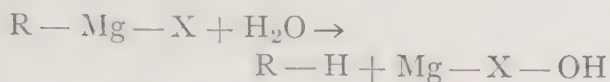
One other aspect of petroleum refining worth mention is "cracking," or pyrolytic decomposition of higher molecular weight hydrocarbons to yield low molecular weight hydrocarbons, more than doubling the yield of gasoline produced by simple distillation refining. Earlier processes of cracking at temperatures up to 700° C. and 1,200 lbs. per sq. in. pressure are being replaced by catalytic cracking methods such as the Houdry process, which operates at 450° C. and 30 lbs. per sq. in. in the presence of an

aluminum silicate and manganese dioxide catalyst. Cracking produces a mixture of low molecular weight paraffinic and olefinic or unsaturated aliphatic hydrocarbons. In catalytic processes, a higher percentage of branched chain alkanes is formed, and the olefines initially produced are polymerized to aromatic hydrocarbons. The end result is a gasoline with a higher combustion engine efficiency rating.

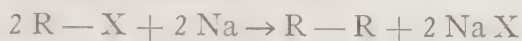
The past few decades have seen a tremendous inroad on our petroleum reserves. The United States, which contains less than one third of the estimated 70 billion barrels of proved reserves throughout the world, produces over 60 per cent of the annual world output. To date, this country alone has consumed nearly 35 billion barrels of petroleum. At the present annual rate of world use, over 3 billion barrels, even the total potential world reserve may not last more than a few decades. Therefore, synthetic fuels from coal are coming into greater prominence, although they are costly at this stage of commercial development. The Fischer-Tropsch process, used in Germany since 1936, and known in this country as the Synthine process,² is based upon the reaction between carbon monoxide and hydrogen (produced from coke and steam at high temperature) in the presence of metallic catalysts such as iron, yielding a mixture of olefines and paraffins. A diverse series of products, including fuels, solvents, lubricants and waxes, similar to petroleum refinery products, has been obtained. The exact nature of the synthesis is not understood, but present researches utilizing radioactive isotopic C¹⁴ are expected to clarify the mechanism of the process and to improve its efficiency, which at present does not warrant more extensive industrial development.

Individual alkane hydrocarbons may be synthesized by a number of methods. A few of the more widely used syntheses are reviewed briefly.

1. HYDROLYSIS OF AN ALKYL GRIGNARD HALIDE.



2. THE WURTZ REACTION.



This reaction gives better yields for hydrocarbons of relatively high molecular weight.

3. ELECTROLYSIS OF CARBOXYLIC ACIDS.



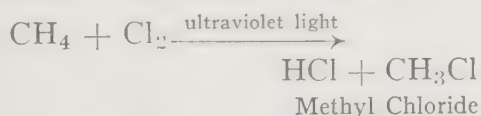
The hydrocarbon and CO_2 are liberated at the anode.

CHEMICAL PROPERTIES

Alkanes undergo pyrolysis, yielding smaller molecules of unsaturated hydrocarbons, hydrogen and carbon.

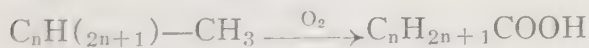
Alkanes generally do not interact with such highly reactive reagents as concentrated sulfuric, nitric acid or potassium permanganate. Nevertheless, it is possible to cause some alkanes to interact under special conditions. The following are illustrative reactions.

1. PHOTOCHEMICAL HALOGENATION.

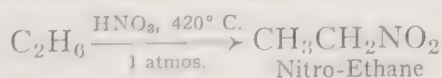


This reaction may be explosive unless concentrations are kept low. The reaction proceeds to the formation of CH_2Cl_2 (methylene chloride), CHCl_3 (chloroform) and CCl_4 (carbon tetrachloride).

2. CONTROLLED AIR OXIDATION. HIGH-BOILING MINERAL OILS MAY BE CONVERTED TO CARBOXYLIC ACIDS.



The acids formed resemble the higher fatty acids, e.g., stearic acid, and have been utilized as fat substitutes in countries deficient in vegetable crops and livestock.

3. VAPOR PHASE NITRATION.³

The nitroparaffins,⁴ a commercial development of the past decade, are valuable industrial solvents and serve as starting materials in the syntheses of unique pharmaceutical emulsifiers and of such therapeutic agents as the sympathomimetic amines.

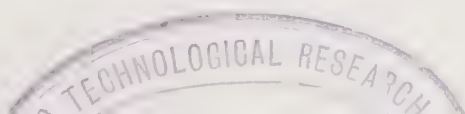
The lower members of the alkane series are of little use in medicine. Attempts to utilize their slight anesthetic properties have proved unsuccessful. As the molecular weight increases, up to C_7H_{16} , there is a concomitant increase in toxicity. Above this molecular weight, the narcotic properties recede rapidly.

USE IN PHARMACY

The alkane products of pharmaceutical interest are mixtures of hydrocarbons derived from petroleum.

Petroleum Benzin (Petroleum Ether, Purified Benzin) U.S.P. Petroleum benzin "is a purified distillate from petroleum, consisting of hydrocarbons, chiefly of the methane series." It has a boiling range of 35 to 80° C. and a specific gravity range of 0.634 to 0.660. It differs from commercial cleaning benzin in being free from fat or other residue. It is highly inflammable and its vapors are explosive. Because of its excellent solvent properties for fixed and volatile oils, it is used as a pharmaceutical extractant and in the defatting of drugs. It is miscible with chloroform, ether, benzene and dehydrated alcohol, and insoluble in water. The latter property permits the clean-cut separation of benzin-soluble active agents from aqueous solutions.

Deodorized Kerosene. The kerosene fraction of petroleum contains aliphatic hydrocarbons from C_9H_{20} to $\text{C}_{15}\text{H}_{32}$ and also some unsaturated hydrocarbons. By treating commercial kerosene with concentrated sulfuric acid and washing, followed by filtration through adsorbent clays such as fuller's earth, a deodorized kerosene is obtained. This, because of its freedom from irritant unsaturated compounds, is used in such



cosmetic preparations as hair oils and brilliantines and in liniments and antiseptic solutions. It is readily miscible with vegetable and mineral oils and evaporates at a very slow rate. It is also used in the manufacture of insecticidal liquids containing pyrethrum extract and D.D.T.

Light Liquid Petrolatum (Light Liquid Paraffin, Light White Mineral Oil) U.S.P. Light liquid petrolatum "is a mixture of liquid hydrocarbons obtained from petroleum." Mineral oils for pharmaceuticals are purified and freed from sulfur compounds, unsaturated hydrocarbons and solid paraffins. They are colorless, nonfluorescent, odorless and tasteless oils, but otherwise analogous to lubricating oils in composition and are composed chiefly of C_{15} to C_{20} hydrocarbons. Most American oils are chiefly aliphatic hydrocarbons. Russian mineral oils contains naphthenes or cyclic polymethylene hydrocarbons, $CH_2-(CH_2)_n-CH_2$, where n may be 1 to 4, and the hydrogen atoms may be substituted by low molecular weight alkyl groups. Naphthenes tend to give greater viscosity to oils than paraffins. In either series, the viscosity and the specific gravity, in general, increase with increased molecular weight. This is the basis of the distinction between light and heavy mineral oils. Light White Mineral Oil has a specific gravity range of 0.828 to 0.880 and a kinematic viscosity, at body temperature ($37.8^\circ C.$), of not more than 37 centistokes (172.7 seconds by Saybolt Universal Viscosimeter).

Light White Mineral Oil is used in cosmetic products such as sun-screen oils, baby oils, hair gloss, and in cleansing creams. It has pharmaceutical application in ointments and nasal preparations. Nose drops and sprays containing mineral oil should be applied cautiously, and preferably under physician's supervision in infants, because of the possibility of aspiration of the oil and subsequent lipoid pneumonia since mineral oil is not readily absorbed in the lungs.

OFFICIAL OCCURRENCE		Per Cent Light White Mineral Oil
U.S.P.		
Cupric Citrate Ointment.....		21.0
N.F.		
Aromatic Spray		97.8
Compound Menthol Spray.....		97.3
Compound Sulfur Ointment.....		6.0
Ephedrine Spray		98.8
Ephedrine Compound Spray.....		97.8
Mild Resorcinol Paste		40.0
Solid Petrox		20.0
Strong Resorcinol Paste.....		40.0

Liquid Petrolatum (Liquid Paraffin, White Mineral Oil, Heavy Liquid Petrolatum) U.S.P. "Liquid petrolatum is a mixture of liquid hydrocarbons obtained from petroleum." It has a specific gravity range of 0.860 to 0.905 and a kinematic viscosity at $37.8^\circ C.$ of not less than 38.1 centistokes (177.2 seconds, Saybolt). Heavy Russian mineral oils may have viscosities in excess of 300 seconds.

Although mineral oil is composed of hydrocarbons of marked stability, some oils, particularly those less highly refined, on exposure to light and air develop a kerosene odor and taste. This is believed to be due to peroxide formation. There is no official test prescribed for measuring the stability of a mineral oil. Golden⁵ has developed a shelf-life test based upon heating the oil for two to fifteen minutes at $300^\circ F.$ and testing for peroxide formation with an acetone solution of ferrous thiocyanate. Those oils withstanding peroxide formation for 15 minutes have an estimated shelf-life of at least a year.

Mineral oil has been widely used as an intestinal lubricant and laxative, and for softening the contents of the lower intestine in the treatment of hemorrhoids and other rectal disturbances. Oils of higher viscosity are desirable because of their lesser tendency to leak out from the lower bowel. Petrolatum is sometimes added further to prevent this. Mineral oil has also been used as a noncaloric oil in obesity diets. Recent studies⁶ have indicated that mineral oil used near mealtime interferes with the absorp-

tion of vitamins A, D and K from the digestive tract and therefore interferes with the utilization of calcium and phosphorus, leaving the user liable to deficiency diseases; when used during pregnancy it predisposes to hemorrhagic diseases of the newborn. Mineral oil should be prescribed for limited periods and be administered only at bedtime. It should be given to infants only upon the advice of a physician. The average dose is one tablespoonful.

OFFICIAL OCCURRENCE	Per Cent Heavy Mineral Oil
U.S.P.	
Mineral Oil Emulsion.....	50.0
N.F.	
Camphorated Phenol	10.0
Mineral Oil Emulsion with Phenolphthalein	50.0
Neocalamine Ointment	10.0

Petrolatum (Petroleum Jelly) U.S.P. "Petrolatum is a purified, semi-solid mixture of hydrocarbons obtained from petroleum." Petrolatum is a colloidal dispersion of aliphatic liquid hydrocarbons in solid hydrocarbons, the disperser being a plastic material known as proto-substance, consisting of noncrystalline, naturally occurring, branched chain paraffinic type hydrocarbons. Without this, a mixture of mineral oil and paraffin would not be stable; the oil would leak out or "sweat." The fact that petrolatum does not produce an oily stain on paper indicates the presence of the oil in the inner phase of the dispersion.

Petrolatum is yellowish to light amber in color. It is soluble in benzene, chloroform, ether, petroleum benzene or in most fixed and volatile oils. It is partly soluble in acetone, the proto-substance being precipitated out. It is insoluble in alcohol or in water.

The melting point ranges from 38 to 60° C. This should not be confused with the consistency of a petrolatum, measured by a penetrometer, which characterizes the firmness of texture. The latter is dependent upon the microscopic fibers which make up a petrolatum. If these are tough and stiff, a very firm consistency results. Fibers may also be short, medium or long. If too short, a soupy

type of product results during summer temperatures. If too long, the petrolatum is too tacky. Medium length is preferred for most pharmaceutical products. Petrolatums of soft consistency are generally used where ease of spreading is desired. Those of medium consistency are the most widely used for ointments and cosmetic creams. Those of hard consistency are used in lipsticks and where considerable mineral oil is to be incorporated.

Petrolatum is miscible with a relatively small proportion of water. However, the addition of small amounts of such ingredients as cetyl alcohol, lanolin and cholesteryl esters⁷ may increase the water absorption properties to nearly ten times the weight of the petrolatum base.

White Petrolatum (White Petroleum Jelly) U.S.P. "White Petrolatum is petrolatum wholly or nearly decolorized." This differs from Petrolatum U.S.P. only in respect to color. It is white or faintly yellowish and transparent in thin layers. This type is preferred as a household topical dressing.

Although many types of dressings have been advocated for burns, petrolatum has been suggested as a simple and effective application. By use of petrolatum on sterile gauze covered with a compression elastic bandage healing of uncomplicated burns has been reduced from seven to two days when compared with other methods of topical treatment.⁸

OFFICIAL OCCURRENCE	Per Cent Petrolatum
U.S.P.	
Ammoniated Mercury Ointment.	81.0
Belladonna Ointment	76.5
Boric Acid Ointment.....	76.5
Chrysarobin Ointment	78.3
Coal Tar Ointment	45.0
Cupric Citrate Ointment	50.6
Ethyl Aminobenzoate Ointment.	85.5
Hydrophilic Ointment	25.0
Hydrophilic Petrolatum	73.0
Mild Mercurial Ointment.....	74.2
Penicillin Ointment	no limitation
Phenol Ointment	86.4
Pine Tar Ointment	31.5
Sulfur Ointment	70.2
Strong Mercurial Ointment.....	11.0
Tannic Acid Ointment.....	49.3

OFFICIAL OCCURRENCE U.S.P.	Per Cent Petrolatum
White Ointment	90.0
Yellow Ointment	90.0
Zinc Oxide Ointment.....	65.7
N.F.	
Alkaline Sulfur Ointment.....	57.0
Benzoic and Salicylic Acid Ointment	77.0
Bismuth Paste	60.0
Calamine Ointment	75.0
Calomel Ointment	35.0
Capsicum Ointment	85.0
Compound Resorcinol Ointment.	25.0
Ichthammol Ointment	80.0
Iodine Ointment	72.0
Lead Oleate Ointment.....	49.0
Lead Plaster Cerate.....	38.0
Neocalamine Ointment	37.5
Nutgall Ointment	70.0
Scarlet Red Ointment.....	50.0
Stramonium Ointment	75.0
Zinc Oxide Paste	50.0
Zinc Oxide Paste with Salicylic Acid	49.0

Paraffin, N.F. (Petrolatum Wax.) "Paraffin is a purified mixture of solid hydrocarbons obtained from petroleum." It is a white, translucent solid of crystalline structure. Its solubility is similar to that of petrolatum. Its melting range is 47 to 65° C. Its main use in pharmacy is to raise the melting point of ointment bases.

OFFICIAL OCCURRENCE N.F.	Per Cent Paraffin
Bismuth Paste	5.0
Capsicum Ointment	10.0

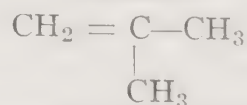
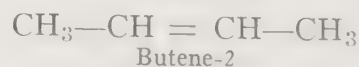
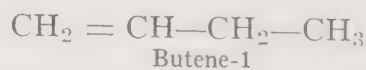
The paraffins of commerce are mainly interlaced plate-type crystals representing straight chain hydrocarbons. Within recent years, paraffinic fractions which consist chiefly of branched chain hydrocarbons have been separated. Physically, they are composed of minute interlacing needles; they are known as microcrystalline waxes. They are higher melting, plastic, tougher and more flexible than regular paraffin. They are used in paper coating, laminated boards and polishes. A pharmaceutical grade of somewhat lower m.p. (55° C.), known as Protowax, is useful to prevent leakage of oils or sweating in lipsticks, ointments and cosmetics.

Ozokerite is a naturally occurring amorphous wax, consisting principally of solid

saturated and unsaturated aliphatic hydrocarbons of high molecular weight. It is found in Austria and Poland, and in this country in Texas and Utah. It comes in its original black color and in bleached yellow and white forms. It differs from paraffin in its higher melting range (up to 80° C.), its greater flexibility and tackiness and its greater shrinkage on solidifying. It is less slippery than paraffin. It has excellent absorbent properties for oils and many volatile solvents. It produces smooth and nongrainy, nonsweaty ointments, cosmetic creams and lipsticks. A purified bleached grade is known as ceresin, although most commercial ceresins are mixtures with more than 50 per cent paraffin.

ALKENES (OLEFINS, ALKYLENES, UNSATURATED ALIPHATIC HYDROCARBONS)

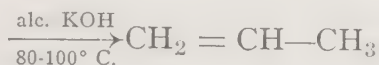
Alkenes have the generic formula C_nH_{2n} . They resemble the paraffins in physical properties, but, in marked contrast, are highly reactive. Structurally, this is indicated by the double bond, $R = R$. The lowest member is ethylene or ethene, $CH_2 = CH_2$. Only one form exists of ethylene, and also of the next member of the homologous series, propene, or propylene, $CH_2 = CH - CH_3$. As the molecular weight increases, two types of isomeric compounds are possible—isomers with respect to the position of the branched chain alkyl substituent and with respect to the position of the double bond or unsaturated linkage. Alkenes are named as are paraffins, the suffix *ane* being replaced by *ylene* or preferably *ene*. The position of the double bond is located by number, using the lowest number of the carbon chain which the bond follows.



2-Methylpropene—1 (Isobutylene)

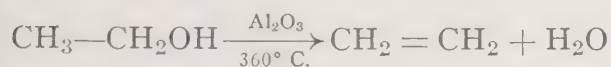
PREPARATION

Alkenes are found in natural gas and petroleum. They are obtained in larger quantities from the latter by "cracking." In the laboratory they usually are prepared by removing hydrogen halide from a halogenated hydrocarbon with alcoholic potassium hydroxide solution.



The yield of propene from 2-iodopropane is 94 per cent in contrast to 36 per cent from 1-iodopropane.

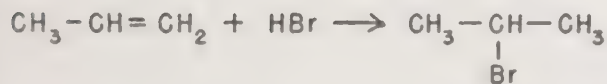
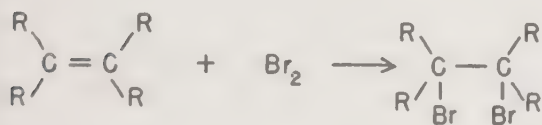
Commercial synthesis is accomplished by the dehydration of alcohols at temperatures of 150° C. or higher in the presence of H_2SO_4 or H_3PO_4 or by alcohols with superheated steam at 360° C. over a catalyst.



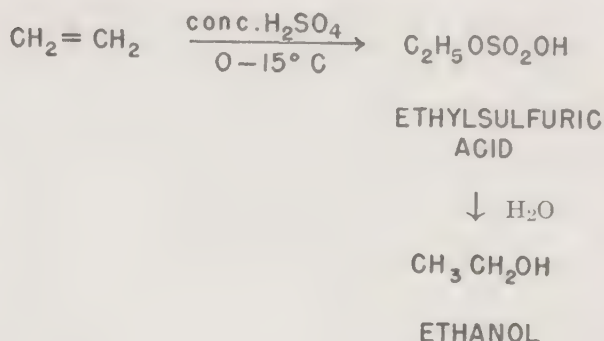
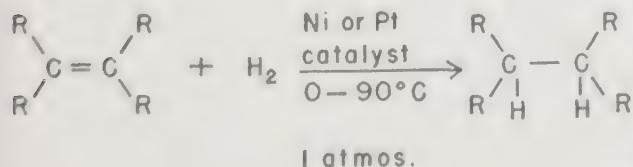
CHEMICAL PROPERTIES

Alkenes are characterized by the following typical reactions.

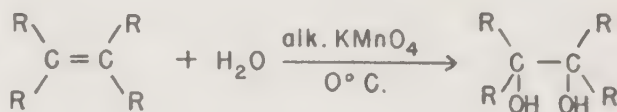
ADDITION AT THE DOUBLE BOND.



In this reaction the halogen becomes affixed to the carbon carrying the smaller number of hydrogen atoms.



OXIDATION TO GLYCOLS.



USE IN PHARMACY

Only the lower members of the alkene series are of pharmaceutical interest.

Ethylene U.S.P. (Ethene). The formula for ethylene is $\text{CH}_2 = \text{CH}_2$. First isolated in 1669, ethylene has become, during the past few decades, the source of a tremendous tonnage of alcohol, ether and other industrial aliphatic derivatives, including many new compounds in the field of solvents and intermediates for the chemical and pharmaceutical industries.

Whether obtained by petroleum "cracking" or catalytic dehydration, the ethylene is purified by fractional distillation of the gas, liquefied at 50 atmospheres and then washed to remove toxic by-products. Later it is compressed into steel cylinders.

Ethylene is a colorless gas of slightly sweet odor and taste. One liter under standard conditions weighs 1.260 Gm. It is soluble in 9 volumes of water and in 0.5 volume alcohol at 25° C. It is highly inflammable, and mixtures with air or oxygen are explosive in the presence of a flame or spark. Ethylene for medicinal use must be free from acetylene, aldehydes, hydrogen sulfide, phosphine and carbon monoxide, and from all but traces of acids, alkalies or carbon dioxide. It is assayed gasometrically by absorption in bromine water.

The introduction of ethylene as an anesthetic arose through the observation in 1908 that the petals of the carnation closed in the presence of illuminating gas and reopened when placed into fresh air within a short interval. The lower alkenes were found to be the major factors in this narcosis. Subsequent toxicity studies on animals by Luckhardt and Carter in 1923 showed that ethylene produced a profound anesthesia. Theories of narcosis and anesthesia are discussed in Chapter Two. Before anesthetics can act as central nervous system depressants, they must first come into close contact with the tissues of the nervous system. Because of the lipoid or fatty character of the cellular constituents, compounds which are excellent fat solvents have been regarded as potential narcotics. They should, however, have a low solubility in aqueous media if they are to be readily released from the blood stream following inhalation or injection. The ratio of the solubility of a drug in lipoids to its solubility in water is designated as the distribution coefficient and serves as one of several yardsticks in the consideration of potential anesthetics. Ethylene has a coefficient of 13.

Ethylene is not altered chemically following inhalation and is eliminated almost entirely from the lungs in a short period. For surgical anesthesia, 80 to 85 per cent ethylene is used admixed with oxygen to remove the asphyxial effects. It is an effective analgesic in obstetrics. It does not relax the abdominal muscles sufficiently for use in intra-abdominal operations. It is superior to ether as a surgical anesthetic. It produces no cyanosis, excessive mucus secretion or sweating; induction and recovery are rapid and there is no postoperative nausea. It is about as explosive as ether when admixed with oxygen, beginning at 1.5 per cent oxygen concentration and being most violently explosive at 74 per cent oxygen concentration. Adequate ventilation and freedom from sparks within a distance of several feet should be maintained. A relative humidity above 55 per

cent is a better safeguard than grounding in the prevention of explosions of electrostatic origin.

In addition to its use as an anesthetic, ethylene has been utilized in the controlled ripening of bananas, citrus fruits, bulbs and potatoes, permitting the shipment of green or unripe crops. It enables starches to hydrolyze to sugars and develops the matured coloring principles.

Propylene (Propene). Propylene, $\text{CH}_2 = \text{CH} - \text{CH}_3$, has physical and chemical properties similar to ethylene, but it is liquefied more readily, its boiling point being -48°C . compared to -104°C . for ethylene. It is also more reactive chemically than ethylene.

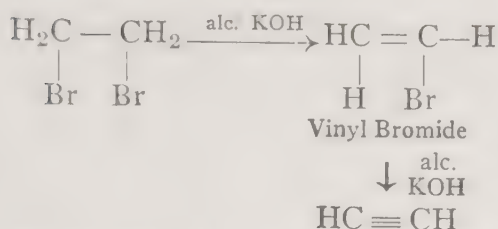
Although it has a higher distribution coefficient (52) than ethylene, propylene has proved more toxic, particularly to the cardiovascular system. This, however, is believed due to impurities rather than to propylene itself. Lack of adequately purified commercial propylene has prevented its successful clinical use. Like ethylene, it is a ripening agent, but it is more costly.

Higher members of this series, such as the butylenes (C_4H_8) and amylenes (C_5H_{10}), are more potent anesthetics, but because of marked initial excitation or depressant action on the circulation, have not been adopted clinically.

ALKINES (ACETYLENES, ETHINES)

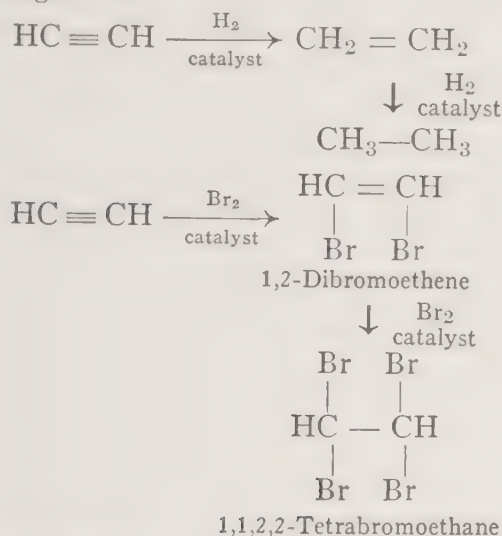
These unsaturated hydrocarbons have the generic formula $\text{C}_n\text{H}_{2n-2}$. Their chemical reactivity is represented structurally by a triple bond, $\text{R} \equiv \text{R}$. The nomenclature is analogous to that of the alkenes, the suffix *ine* or *yne* being used.

Acetylene (Ethine, Narcylene), $\text{HC} \equiv \text{HC}$, the lowest member of the group, typifies many of the reactions of the group. It is found in illuminating gas and is formed in larger quantities by incomplete combustion when a Bunsen burner "strikes back," producing a flame at the base. Acetylene may be synthesized from 1,2-dibromoethane.



Commercially, it is made by the action of water on calcium carbide, CaC_2 , or by passing hydrogen through an electric arc.

It reacts stepwise with hydrogen or halogen:



Acetylene forms explosive acetylides with salts of some heavy metals such as copper or silver ($\text{H} - \text{C} \equiv \text{C} - \text{Ag}$). When passed over quartz catalyst at 160°C ., it forms the aromatic hydrocarbon benzene, C_6H_6 . In the presence of copper catalyst, it adds to itself (polymerizes), forming vinylacetylene, $\text{CH}_2 = \text{CH} - \text{C} \equiv \text{CH}$, and higher polymers.

Acetylene is a colorless gas with a garlic-like odor. Because of its tendency to explode when compressed, it is available commercially, dissolved under 200 lbs. pressure in acetone; 300 volumes dissolve in 1 volume of acetone.

Its distribution coefficient is 2.2. It is effective for surgical anesthesia at a concentration of 70 to 80 per cent. Its explosive range is 2.8 to 85 per cent when admixed with oxygen. Its extensive use as an anesthetic has, in part, been precluded by the need for washing out the acetone from the commercially available form.

Acetylene is the basis for a host of industrial chemicals and intermediates, including polymerized products such as Neoprene, a synthetic rubber.

DIENES OR DIOLEFINS.

These aliphatic hydrocarbons ($\text{C}_n\text{H}_{2n-2}$), that contain two unsaturated linkages, are classified on the basis of the position of the double bonds; (1) those in which the double bonds are adjacent, such as allene ($\text{CH}_2 = \text{C} = \text{CH}_2$) and its homologues, (2) those in which the double bonds are conjugated or separated by a single bond, such as butadiene - 1,3 ($\text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2$), (3) those in which at least two single bonds separate the double bonds, such as penta-diene - 1,4 ($\text{CH}_2 = \text{CH} - \text{CH}_2 - \text{CH} = \text{CH}_2$).

Dienes do not include any compounds of pharmaceutical interest, although diene linkages are encountered as side chains in some drug components. Conjugated dienes form addition products with maleic anhydride, a double bond shifting to the 2,3 position. This is known as the Diels-Alder reaction and is used in the synthesis of some medicinal compounds, such as vitamin K analogues.

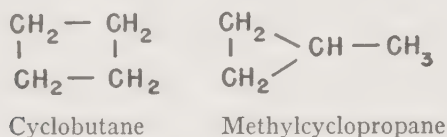
Industrially, isoprene (2-methylbutadiene - 1,3) is the most important diolefine, being the unit hydrocarbon of natural rubber. It may be polymerized readily to form a rubber having most of the properties of the natural product.

CYCLOPARAFFINS (POLYMETHYLENES, NAPHTHENES, ALICYCLIC HYDROCARBONS)

These hydrocarbons (C_nH_{2n}), though ringed or closed chain, bear a closer resemblance to the paraffins than to the benzenoid hydrocarbons. The carbon valences are fully saturated. Based on the Bayer strain theory, the five- and six-carbon rings are most stable; the three- and four-membered rings are more reactive and deviate in properties from the other members of the series.

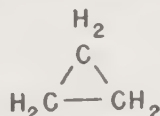
Nomenclature resembles that of the paraffins, the prefix *cyclo* being used to designate

the closed part of the molecule. Typical isomeric compounds are represented as follows:



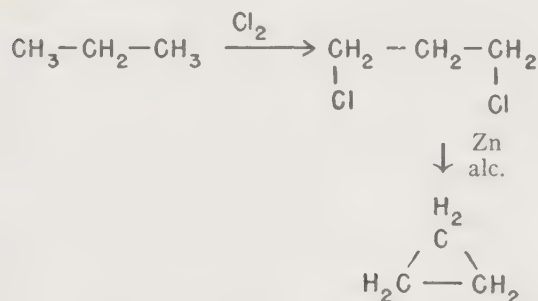
Only one cycloparaffin is official in the U.S.P.

Cyclopropane (Trimethylene) U.S.P.



This was first isolated in 1882, but it was not until 1929 that its study as an impurity in propane led to its use as a valuable inhalation type anesthetic.

It may be prepared commercially in pure form for anesthetic use by the following reactions.



Cyclopropane is a colorless gas, resembling petroleum benzin in odor though somewhat sweeter, and having a pungent taste. It is slightly soluble in water, and freely soluble in alcohol or fixed oils. One liter weighs 1.879 Gm. at 0° C. and 760 mm. It liquefies at 75 lbs. pressure at 20° C. and boils at -34° C. It is marketed in compressed form in cylinders. It diffuses readily through rubber hose.

Like ethylene, cyclopropane is inflammable and forms explosive mixtures with oxygen. It is resistant to oxidation by potassium permanganate. It does not form addition products with iodine. Bromine opens the ring, forming 1,3-dibromopropane. Hydrogen bromide forms monobromopropane. Iron, at a temperature only slightly

above that of a warm room, catalyzes cyclopropane to form small amounts of propylene. At 100° C. there is more than a 50 per cent conversion. Improper storage conditions in iron cylinders therefore may markedly affect its safe utilization. The U.S.P. prescribes tests for propylene and other unsaturated hydrocarbons, as well as for CO, CO₂, halogens, acids and alkalies.

As a general anesthetic, it compares favorably with ethylene, having three times the distribution coefficient of the latter. It is used in 15 to 30 per cent concentration, admixed with oxygen, for initial anesthesia, and in 4 per cent concentration for maintenance. For economy it is rebreathed after washing through soda lime. It is more diffusible than ethylene and is eliminated from the body more slowly than ethylene but more rapidly than ether. It is pleasant to take and has relatively few objectionable after-effects. Because it is nonirritant, it produces no laryngospasm and may cause respiratory failure before circulatory collapse. It is, therefore, frequently administered with mixtures of 5 to 30 per cent carbon dioxide in oxygen to provide stimulation of the respiratory reflex.

Higher homologues of cyclopropane, up to about C₁₀ compounds, show increased anesthetic potency, but such side effects as increased muscular tonus and cardiovascular disturbances have precluded their use.

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ABRAHAM TAUB, A.M.

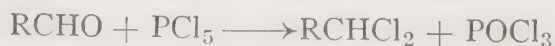
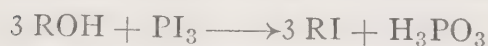
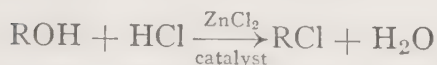
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5

Aliphatic Halogenated Compounds

ALKANE DERIVATIVES

One or more of the hydrogen atoms of paraffin hydrocarbons may be replaced by chlorine, bromine, iodine or fluorine, although not necessarily by direct substitution. Halogenated hydrocarbons do not occur naturally. In addition to the methods of direct substitution of saturated hydrocarbons and of addition of halides or hydrogen halides to unsaturated hydrocarbons (discussed in Chap. 4), halogenated hydrocarbons may be prepared by the interaction of alcohols, aldehydes or ketones with hydrogen halides, phosphorus halides or thionyl chloride (SOCl_2).

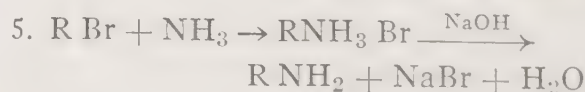
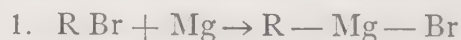


Halogens in hydrocarbons increase their specific gravity and raise their boiling points. The iodine derivatives have the highest boiling points and the bromine derivatives intermediate boiling points compared to those of the chlorinated hydrocarbons of analogous structure. Corresponding fluorinated hydrocarbons have the lowest boiling points.

ALKENE DERIVATIVES

All are immiscible with water, although the presence of the halogen atom confers some polar properties upon these compounds. They are less inflammable than the corresponding hydrocarbons and become noninflammable as the degree of halogenation reaches a maximum.

Their reactions in forming saturated and unsaturated hydrocarbons have been discussed previously. Other characteristic reactions include the formation of the (1) Grignard reagent (R-Mg-X), (2) nitriles (organic cyanides), (3) alcohols, (4) ethers from metallic alcoholates and (5) amines.



ALKANE DERIVATIVES

Methyl Chloride (Monochloromethane). Methyl chloride (CH_3Cl) is prepared industrially by the vapor phase chlorination of methane above 200°C . It is a gas of

ethereal odor, having a boiling point of -23.7°C . It burns with a greenish flame. It is easily compressed to a liquid of specific gravity 1.782. When evaporated rapidly in a current of air, a temperature of -55°C . may be obtained. Upon this property depends its rather limited use as a local anesthetic. To avoid blister formation it is generally mixed with ethyl chloride and sprayed directly on the skin or applied with cotton.

The narcotic potency of hydrocarbons increases with the extent of halogenation. Methyl chloride has the lowest and carbon tetrachloride the highest narcotic potency of the chlorinated methanes. Methyl chloride is considered a fair general anesthetic, but it does not produce complete muscular relaxation. More effective and less toxic anesthetics have largely replaced it. When used clinically, it is admixed with ethyl chloride or bromide.

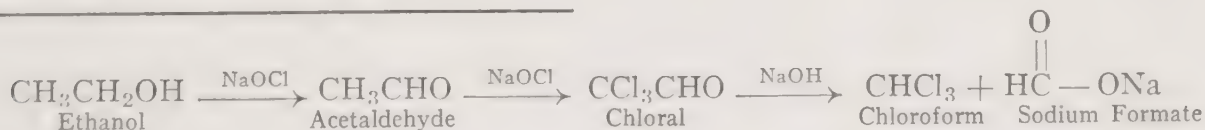
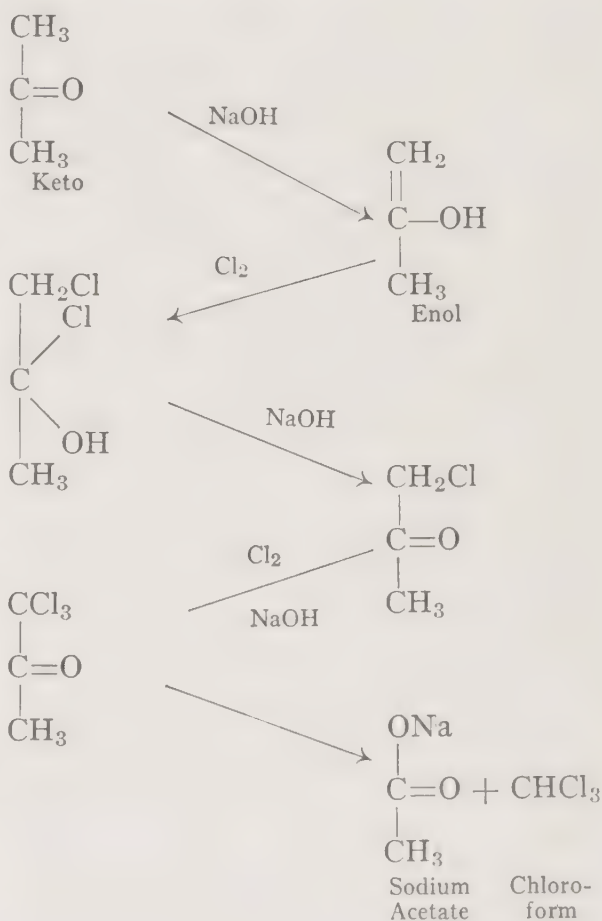
The use of methyl chloride as an industrial refrigerant has been discontinued because of the toxic effects produced by prolonged exposure, as from pipe leaks; as little as 75 parts per million may prove fatal after 72 hours exposure.

Methylene Chloride (Dichloromethane). Methylene chloride (CH_2Cl_2) is a liquid of boiling point 40.8°C . and specific gravity of 1.336. Its vapors are not inflammable, although weakly combustible mixtures are formed with air.

Although methylene chloride is more effective and less toxic as a general anesthetic than methyl chloride, it does not compare favorably with chloroform.

Chloroform (CHCl_3) was first synthesized by Leibig in 1831; it was introduced as an obstetric anesthetic in 1847 by Simpson, an Edinburgh surgeon, within a year of the introduction of ether as an anesthetic in this country.

Chloroform is prepared industrially by the haloform reaction, the starting materials being alcohol or acetone and an alkali chlorine compound such as bleaching powder or sodium hypochlorite.



Methylene chloride is an excellent solvent for oils, rubber, some resins and cellulose plastics. It enters the composition of many paint and varnish removers.

Chloroform U.S.P. (Trichloromethane).

Another commercial synthesis involves the reduction of carbon tetrachloride with iron and water.



Chloroform is a colorless, mobile liquid of ethereal odor and sweet taste. It has a boiling point of 61° C. and a specific gravity of 1.475. It is soluble in about 200 volumes of water and miscible with most organic solvents and oils. Its heated vapors burn with a green flame; the liquid itself is not inflammable. In the presence of air, sunlight or open flames, it is oxidized to phosgene, $\text{Cl}-\text{C}=\text{O}$, a highly reactive gas which hydrolyzes in the lung tissues to hydrogen chloride, producing pulmonary edema. To minimize the existence of phosgene in chloroform during storage, the U.S.P. prescribes the presence of 0.5 to 1 per cent of alcohol. Other impurities that should be absent from anesthetic grade chloroform are chlorine and chlorinated decomposition products, acids, aldehydes, ketones and readily carbonizable substances. Chloroform should be stored in airtight, light-resistant containers at a temperature not above 30° C. When corks are used, they should be covered with tin foil.

Chloroform has a high distribution coefficient (100) between lipoids and water and exhibits anesthetic properties at 1.5 per cent concentration in the air breathed. It is about five times as effective an anesthetic as ether. It does not form explosive mixtures with oxygen. For the most part, it is eliminated unchanged from the lungs. However, some decomposition is believed to occur in the tissues. Although it still is employed as an inhalation anesthetic, its relatively toxic properties have resulted in reduced usage within the past few decades. The incidence of anesthetic cause of mortality has been estimated at 1 per 2,500 for chloroform compared to 1 per 10,000 for ether. Its toxic action is exerted upon the kidneys, the liver and the heart. It stimulates the vagus nerve, slowing the heart. Simultaneously, it causes the production of epinephrine, producing cardiac acceleration. The simultaneous depression and stimulation give rise to an

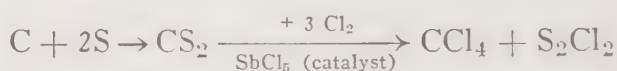
auricular and ventricular fibrillation, which may terminate fatally during the induction stage of anesthesia.

Chloroform is used as a hypnotic and sedative in cough liquids and lozenges and as a counterirritant and analgesic in liniments. Chloroform water is used as a carminative in a dose of 15 cc. It also is used as a preservative for crude drugs and galenicals. It serves as a solvent for fats, resins and some plastics, and is an excellent extractant for alkaloids and other soluble medicinal agents in their manufacture and assay.

The average dose is 0.3 cc.

OFFICIAL OCCURRENCE	Per Cent Chloroform
U.S.P.	
Chloroform Liniment	30.0
Chrysarobin Ointment	7.0
N.F.	
Chloroform Spirit	6.0
Chloroform Water	saturated solution
Chloroformic Coal Tar Solution	95.0
Compound White Pine Syrup	0.6
Elixir Ammonium Valerate..	0.2

Carbon Tetrachloride N.F. (Tetrachloromethane). Carbon tetrachloride (CCl_4) is prepared commercially by the chlorination of carbon bisulfide, the latter being prepared by heating sulfur and coke in an electric furnace.



It is a colorless, mobile liquid, specific gravity 1.590, boiling point 77° C. Like chloroform, it is miscible with alcohol, ether and most organic solvents as well as with fixed and volatile oils. The absence of hydrogen from the molecule of this chlorinated hydrocarbon makes it completely noninflammable and accounts for its use as a fire extinguisher. It should not, however, be used on hot metal or in confined quarters since it forms the toxic phosgene. Occasional explosions have also been reported. The vapors of carbon tetrachloride, like those of all chlorinated hydrocarbons, are toxic. When used as a dry cleaner or an industrial solvent, the atmospheric concentration

should be kept below 100 parts per million for safety. Initial toxic effects are manifested in headache, nausea, abdominal pain and diarrhea. Cumulative effects are marked in the liver, the heart and the kidneys. Although carbon tetrachloride possesses anesthetic properties, its narrow margin of safety precludes its use for this purpose.

Carbon tetrachloride was the first halogenated hydrocarbon to be used as an anthelmintic in hookworm disease, having been introduced by Hall¹ in 1921. Dosage is always followed by a purgative to remove dead worms as well as excess drug. Carbon tetrachloride is capable of causing liver necrosis. This can be combated to an extent by oral or intravenous calcium gluconate. The drug should not be administered during pregnancy because of the liver and kidney damage it produces in the fetus.

The average dose for adults is 2.5 cc.

OFFICIAL OCCURRENCE N.F.	Per Cent Carbon Tetrachloride
Carbon Tetrachloride Capsules	100.0

Methyl Bromide. Methyl bromide (CH_3Br) is a colorless gas; when compressed it forms a colorless noninflammable liquid boiling at 4.5°C . It is used in fire extinguishers; in the presence of flames or hot surfaces, hydrogen bromide and bromine are liberated. Because of the excellent penetration of the gas, it has been used effectively as a fumigant to combat insect pests in grains and other foodstuffs, and crude drugs. It is also used as a rodenticide. Its vapors are toxic to the nervous system.²

Bromoform (Tribromomethane). Bromoform (CHBr_3) is a colorless liquid, boiling at 150°C . In many respects it resembles chloroform, the noteworthy exception being its high specific gravity, 2.9. This property is utilized in flotation separation in mineral analysis. The presence of 3 per cent alcohol in bromoform retards its tendency to liberate bromine and form brominated decomposition products. Although it has narcotic properties, its low vapor pressure and toxicity limit its use as an anesthetic. Therapeu-

tically, it has been advocated as a sedative in whooping cough and in seasickness remedies in dosages of 0.06 to 0.33 cc. administered in capsules or in emulsion of olive oil. Its toxic effects upon the heart have limited its use. It is obsolescent as a therapeutic agent.

Methyl Iodide (CH_3I) is a relatively unstable, colorless liquid having a specific gravity of 2.28 and boiling at 44°C . It liberates iodine on exposure to light. Like methyl bromide, its vapors are insecticidal, but its cost precludes its use as a fumigant. It is used in organic synthesis for introducing methyl groups.

Iodoform (Tri-iodomethane) N.F. The haloform synthesis of iodoform (CHI_3) from alcohol or acetone, alkali and iodine is also the basis of the sensitive Lieben iodoform test for the presence of $\text{CH}_3\text{CHOH-}$ or $\text{CH}_3\text{CO-}$ groups. Commercially, it is prepared by the electrolysis of an aqueous solution of sodium iodide, sodium carbonate and alcohol.

Iodoform is a greenish-yellow, crystalline powder with a penetrating persistent odor. It is slightly volatile at 25°C . It melts at 115°C . and emits vapors of iodine at higher temperature. It is insoluble in water, sparingly soluble in alcohol or glycerin and soluble in ether, chloroform or fixed oils. Its use as a dusting powder on wounds is dependent upon the slow liberation of iodine. Attempts to disguise its odor with thymol or paraformaldehyde have not prevented its becoming obsolescent. Odorless antiseptic compounds have largely replaced it.

Difluordichloromethane (Freon). Difluordichloromethane (CF_2Cl_2) is a unique gaseous halogenated hydrocarbon. It is synthesized commercially from hydrogen fluoride and carbon tetrachloride in the presence of antimony pentachloride and trifluoride. Freon is illustrative of the stabilizing effect produced by introducing more than one fluorine atom into hydrocarbons containing other halogen atoms. This is believed to decrease distances between carbon and halogen atoms. In contrast to CH_3F ,

CH_3Cl or CCl_4 , freon is remarkably stable to hydrolysis and to temperatures up to 550°C . It does not react with metallic sodium. Because of its low boiling point (-30°C), noninflammability and unexpected freedom from toxicity, Midgley and Henne³ introduced it as a refrigerant in 1930. Tests by the U. S. Bureau of Mines have shown it to be nontoxic at concentrations of 20 per cent in air for exposures as long as eight hours. It has been widely adopted in the closed systems of mechanical refrigerators.

Ethyl Chloride U.S.P. (Monochloroethane, Kelene). Although gaseous at room temperature (b.p. 12°C), ethyl chloride ($\text{CH}_3\text{CH}_2\text{Cl}$) is available in liquefied form in valved glass or metal cylinders. In its liquefied state it has a specific gravity of 0.921 at 0°C . It has an ethereal odor and burning taste. It is slightly soluble in water and soluble in alcohol and in ether. It is inflammable and explosive when present in as little as a 4 per cent concentration in air. When sprayed on the unbroken skin, a temperature of -20°C . results, causing the tissues to freeze and producing local insensitivity to pain for short periods. It has proved effective in rapid recovery of use of sprained joints.

Ethyl chloride was introduced by Carlson in 1894 as a general inhalation anesthetic in dentistry. It is used in concentrations of 3 to 5 per cent, and is eliminated unchanged from the lungs. Its use is limited to operations of short duration and for induction of anesthesia prior to ether administration. Its use as a general anesthetic is accompanied by the same shortcomings that characterize chloroform. Industrially, ethyl chloride is used in the synthesis of tetraethyl lead, a component of "Ethyl" gasoline.

Ethylene Chloride ("Oil of Dutch Chemists"). Ethylene chloride ($\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$) is synthesized commercially from liquid chlorine and dry ethylene. It has a specific gravity of 1.26 and a boiling point of 84°C .; it is immiscible with water.

It is a chemically stable compound and is

noncombustible. It is a liquid of high solvent power and is used in dry cleaning, extraction, and fumigation. It is the starting material for thiokol, a rubber substitute, for colorless Vinylite plastics and for a host of industrial products.⁴

Although its anesthetic properties resemble those of chloroform, it has not been adopted clinically.

An isomeric compound, *ethylidene chloride*, 1,1-dichloroethane, $\text{CHCl}_2-\text{CH}_3$, is prepared from acetaldehyde and phosphorus pentachloride. It has a boiling point of 58°C . and a specific gravity of 1.17. It has good solvent properties but is much less used than ethylene chloride. It is a more potent anesthetic than chloroform or ethylene chloride, but is more toxic.

Ethyl Bromide. Ethyl bromide ($\text{CH}_3-\text{CH}_2\text{Br}$) is a colorless liquid of specific gravity 1.43 and boiling point 38°C . It has an ethereal odor and sharp, burning taste. It is only sparingly soluble in water, but is soluble in alcohol and in ether. It is used as a refrigerant topical anesthetic like ethyl chloride; it also is used for temporary relief from neuralgia. In admixture with methyl and ethyl chlorides it has been used for general anesthesia. This use is limited because of the slow decomposition of ethyl bromide to bromine in the presence of air and light.

Chlorinated Paraffin (Chlorcosane) N.F. "Chlorinated Paraffin is a liquid paraffin which has been treated with chlorine."

Chlorinated paraffin is made by passing chlorine into melted paraffin at 135°C . The reaction is stopped when 30 to 40 per cent of chlorine is present. Halogen-substituted paraffin hydrocarbons are formed. Traces of free chlorine are removed with dry sodium carbonate and subsequent filtration.

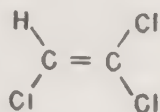
It is an odorless, viscous liquid, yellow to amber in color, with a specific gravity of 1.03. It is not miscible with water, is slightly soluble in alcohol and is miscible with ether, chloroform or benzene.

Chlorcosane was introduced by Dakin in 1918 as a special solvent for Dichloramine T since this decomposes in mineral oil. Con-

centrations up to 8 per cent may be made. If the solution is to be used as a spray on wounds, it may be diluted with 10 per cent of carbon tetrachloride.

ALKENE DERIVATIVES

Trichloroethylene U.S.P. (1,1,2-Trichloroethene).



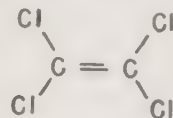
Trichloroethylene is made by elimination of hydrogen chloride from symmetrical tetrachlorethane ($\text{CHCl}_2 \cdot \text{CHCl}_2$) by passing the latter over hydrated lime, or over pumice at 500°C .

The U.S.P. product contains 0.5 per cent alcohol and may contain 0.02 per cent ammonium carbonate as a preservative. It decomposes in the presence of light and moisture.

Trichloroethylene is a colorless mobile highly volatile liquid with a specific gravity 1.46 and a boiling point of 88°C .

The extensive use of trichloroethylene in industry as a solvent and dry cleaner led to the observation that upon prolonged exposure it exerted an anesthetic effect upon the sensory endings of the trigeminal nerve, widely distributed in the tissues of the face. It has been used effectively in the alleviation of trigeminal and other facial neuralgias. For this purpose it is available in hermetically sealed fragile glass tubes, covered with fabric. The permissible use of ammonium carbonate is to prevent thermal decomposition during sealing. The dosage is 1 cc., one to three times daily. The tube is crushed at the bottom of a tumbler, and the patient inhales the vapors. Trichloroethylene is also used in the prevention and treatment of attacks of angina pectoris. It is not, however, a substitute for amyl nitrite. Trichloroethylene is a general inhalation anesthetic but its promotion of increased muscular activity and of cardiac irregularities limit its use.

Tetrachloroethylene (Perchloroethylene) U.S.P. (Tetrachloroethene.)



Tetrachloroethylene may be synthesized from dry hydrogen chloride and carbon monoxide at 300°C . and 200 atmospheres pressure in the presence of a nickelous oxide catalyst, or by passing symmetrical ethylene dichloride and chlorine over heated pumice at 400°C .

Tetrachloroethylene is a colorless, mobile liquid of ethereal odor with a specific gravity of 1.61 and a boiling point of 122°C . It is miscible with an equal volume of alcohol and with most organic solvents. Like the trichloroethylene, it is unstable to air, moisture and light, decomposing in part to phosgene and hydrochloric acid. The U.S.P. permits up to 1 per cent alcohol as preservative. It is noninflammable. It is used industrially as a solvent and as a textile and metal cleaner.

Although it is a potent anesthetic, it is a skin and respiratory irritant and difficult to vaporize. Its specific use in medicine is as an anthelmintic in hookworm infestation. Wright and Schaffer,⁵ in their attempt to correlate anthelmintic efficiency of chlorinated alkyl hydrocarbons and chemical structure, observed the following trends: in any one homologous series anthelmintic efficiency increases with the lengthening of the carbon chain; correspondingly, there is a decrease in water solubility, about 1:1,000 to 1:5,000, for most effective anthelmintic compounds; the optimum range varies for different homologous series. Substitution of bromine or iodine for chlorine makes less difference in anthelmintic efficiency than does change in water solubility; the optimum solubility range for these halogenated hydrocarbons is 1:1,000 to 1:1,700.

All of these compounds are irritant to the gastro-intestinal tract and produce varying degrees of liver and kidney degeneration. Tetrachloroethylene is about equally as ef-

ficient as carbon tetrachloride, and is preferred in hookworm treatment because it is less toxic and does not raise the guanidine content of the blood, a criterion of importance where calcium deficiency exists.

The dosage is 1 to 3 cc. This may be given on sugar or in gelatin capsules after first emptying the gastro-intestinal tract. It is followed by a saline cathartic. Oils, fats and alcohol favor absorption and toxic side effects, and therefore, should be avoided.

OFFICIAL OCCURRENCE U.S.P.	Per Cent Tetra- chloroethylene
Capsules Tetrachloroethylene. .	100.0

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6

Aliphatic Hydroxy-Containing Compounds

MONOHYDRIC ALCOHOLS

MONOHYDRIC HALOGENATED ALCOHOLS

DIHYDRIC ALCOHOLS (GLYCOLS)

TRIHYDRIC ALCOHOLS

GLYCEROPHOSPHATES

POLYHYDRIC ALCOHOLS

UNSATURATED ALCOHOLS

The aliphatic hydroxy-containing compounds included in this chapter are the monohydric alcohols, the monohydric halogenated alcohols, the dihydric alcohols, the trihydric alcohols, the polyhydric alcohols and the unsaturated alcohols.

Alcohols possess properties similar to those of both hydrocarbons and water and may be considered as derivatives of either. Water (H-O-H) with one of its hydrogen atoms replaced by a hydrocarbon yields a monohydric alcohol. A hydrocarbon with one of its hydrogen atoms replaced by a hydroxyl group yields a monohydric alcohol.

Hydrocarbons undergo a decided change in physical, chemical and physiologic properties when one or more hydroxyl groups are introduced. The physical properties approach those of water, especially in the alcohols of low molecular weight. These are readily water-soluble. However, water-solubility decreases as the molecular weight of the alcohol increases and is increased with an increase in the number of hydroxyl groups and the branching of the chain. Therefore, it is of interest to note that secondary alcohols are more soluble in water than are

the corresponding primary alcohols and that tertiary alcohols are more soluble than secondary ones. Alcohols have solvent powers similar to those of water and hydrocarbons; this is particularly true of methanol, ethanol, isopropanol, glycol and glycerin. The similarity to the solvent powers of hydrocarbons increases with an increase in the molecular weight. In a given carbon chain, as the hydroxyl groups are increased, so is the boiling point, the sweetness and the solubility in water.

There are three types of monohydric alcohols, depending upon the number of chemical groups attached to the same carbon atom bearing the hydroxyl group. A primary alcohol ($R-CH_2OH$) has one R group and two hydrogens attached to the hydroxyl carbon; a secondary alcohol (R_2CHOH) has two R groups and one hydrogen attached to the hydroxyl carbon; a tertiary alcohol (R_3COH) does not have any hydrogen attached to the carbon atom to which the hydroxyl is attached.

Alicyclic alcohols are formed from cyclic hydrocarbons by replacing one or more hydrogen atoms by a hydroxyl group. These

are usually secondary alcohols. A phenol is an aromatic compound that has a hydroxyl group attached to an aromatic ring. In any chemical structure, a carbon atom rarely bears two hydroxyl groups. Glycols are aliphatic alcohols containing two hydroxyl groups, e.g., ethylene glycol. There occur in nature compounds having two or more hydroxyl groups (glycerin and mannitol) as well as compounds containing several hydroxyl groups along with other chemical groups such as aldehyde (glucose), carboxyl (uronic acids) and amino (glucosamine).

Alcohols in the form of esters are widely distributed in nature. Volatile oils, fixed oils, fats, waxes, etc. are the most common sources of these alcohols.

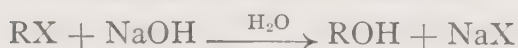
MONOHYDRIC ALCOHOLS

PREPARATION

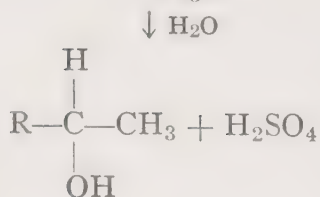
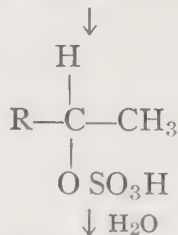
The availability of alcohols is most varied; some are obtained from natural sources (glycerin from fat), some are prepared from complex natural material by fermentation processes (ethanol from starch), some are prepared by synthesis from simple chemicals (methanol from hydrogen and carbon monoxide) and others from standard procedures in organic chemistry (isopropyl alcohol by the reduction of acetone).

Methods applicable to the preparation of monohydric alcohols follow.

1. HYDROLYSIS OF ALKYL HALIDES.

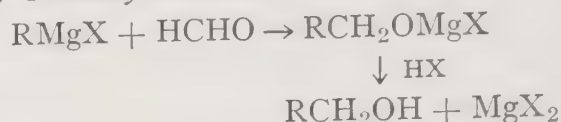


2. HYDRATION OF ALKENES.

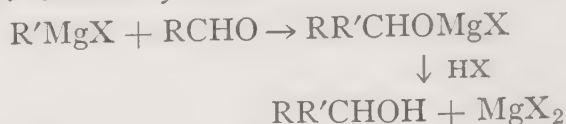


3. GRIGNARD SYNTHESIS. In this process, an alkyl group and a hydrogen are introduced into a carbonyl compound, thus providing a source of primary, secondary or tertiary alcohols.

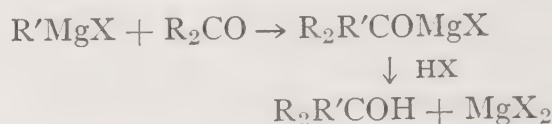
a. Primary Alcohol.



b. Secondary Alcohol.

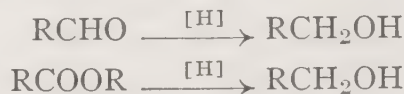


c. Tertiary Alcohol.



4. HYDROGENATION OR REDUCTION OF ALDEHYDES, KETONES OR ESTERS.

a. Primary Alcohols.



b. Secondary Alcohols.



5. SPECIFIC METHODS ADAPTABLE TO INDIVIDUAL ALCOHOLS (q.v.).

Methods applicable to the preparation of dihydric alcohols are discussed in connection with ethylene glycol. Procedures used to obtain trihydric and polyhydric alcohols are limited in number, and examples are given for the specific alcohols later described.

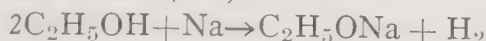
CHEMICAL PROPERTIES

In chemical properties, the alcohols of lower molecular weight resemble water by reacting with halides of sodium and phosphorus. They are neutral to litmus paper and often form, with organic salts, a complex called "alcohol of crystallization." Their chemical properties approach those of the hydrocarbons as the molecular weight increases and those of water as the number of hydroxyl groups increases. A hydroxyl group introduced into a hydrocarbon pro-

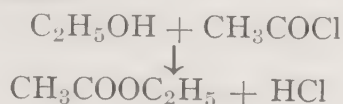
duces a class of compounds, alcohols, that exhibit individual chemical properties. Some of these properties are reaction with metals to form metal alkylates, dehydration to form olefins, oxidation to form aldehydes and ketones and combination with acids to form esters.

1. THE HYDROGEN ATOM OF THE HYDROXYL GROUP REACTS WITH THE FOLLOWING TYPES OF CHEMICALS:

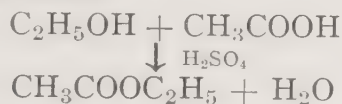
Active Metals (Na).



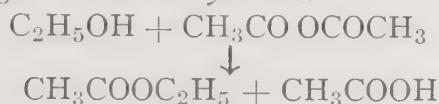
Acid Halides.



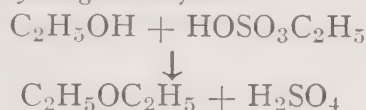
Organic Acids.



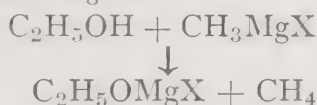
Organic Acid Anhydrides.



Alkyl Hydrogen Sulfates.



Grignard Reagents.

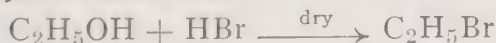


2. THE HYDROXYL GROUP OF ALCOHOLS REACTS WITH, AND IS REPLACED BY, THE FOLLOWING CHEMICALS:

Hydriodic Acid.



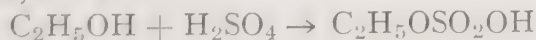
Hydrobromic Acid.



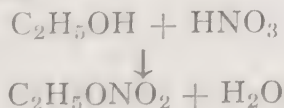
Hydrochloric Acid.



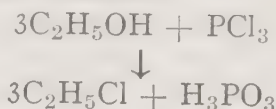
Sulfuric Acid.



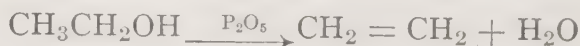
Nitric Acid.



Phosphorous Trihalides.



3. DEHYDRATION. Dehydration of an alcohol, the removal of a molecule of water, produces olefins and may be accomplished with sulfuric acid or phosphorus pentoxide.

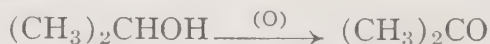


4. OXIDATION. Oxidation of alcohols may be carried out by several procedures, using a variety of oxidizing agents.

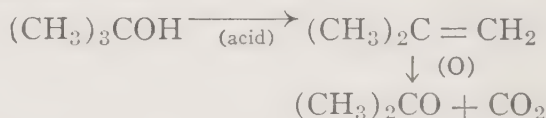
a. *Primary alcohols* are oxidized to aldehydes and then to organic acids.



b. *Secondary alcohols* are oxidized to ketones containing the same number of carbon atoms.



c. *Tertiary alcohols* are more difficult to oxidize; they produce ketones or acids containing fewer carbon atoms than does the original alcohol.



PHYSIOLOGIC ACTION AND CHEMICAL STRUCTURE

Introduction of hydroxyl groups into a chemical structure can be expected to decrease the activity and toxicity of the parent compound. An aliphatic hydrocarbon is decreased in narcotic potency by the substitution of a hydroxyl group for a hydrogen atom. If more than one hydroxyl group is introduced, practically all the characteristic physiologic action is lost (ethane > ethanol > glycol). An aromatic structure having a hydroxyl group is a phenol; these compounds do not have a narcotic effect but are distinctly poisonous to cells.

In Table 8 several alcohols are compared with ethyl alcohol as 1 and are rated in narcotic potency and toxicity. It is observed that both properties increase with an increase in molecular weight.

TABLE 8. RELATIVE TOXICITY AND NARCOTIC POTENCIES OF VARIOUS ALCOHOLS*

ALCOHOL	TOXICITY	NARCOTIC POTENCY
Methanol	0.59	0.53
Ethanol	1.00	1.00
Propanol	2.33	3.27
Butanol	3.56	6.02
Amyl Alcohol	5.99	6.59

* After Lehman, J.: J. Pharmacol. & Exper. Therap. 61:103, 1937.

Increases in toxicity and potency occur as the number of carbon atoms is increased to 8; alcohols with 9 to 16 carbon atoms show a decrease in these properties, and where there are more than 16 carbon atoms, the alcohols are inert. This observation was made many years ago and is known as Richardson's rule. The potency of the alcohols increases in the following order: glycols < primary < secondary < tertiary. Glycol is an exception because of the formation of oxalic acid in the body. Unsaturation usually increases both potency and toxicity. Allyl alcohol is more potent than propanol, but it is a lacrimator and an irritant. Secondary and tertiary alcohols increase in activity as the molecular weight increases, as far as compounds with 6 to 8 carbon atoms, e.g., tertiary amyl alcohol (amylene hydrate) possesses mild hypnotic properties (see Table 9).

TABLE 9. SOPORIFIC PROPERTIES OF VARIOUS ALCOHOLS

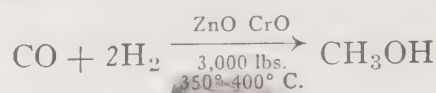
ALCOHOL	HOURS OF SLEEP	
	SECONDARY	TERTIARY
Butyl	3	5
Amyl	2	9
Heptyl	3-4	10-12

Alcohols with branched chains, whether primary, secondary or tertiary, show an increase in volatility and a decrease in narcotic activity.

Substitution of halogens in alcohols has a marked effect on narcotic potency; this is

discussed with the halogenated alcohols (q.v.).

Methyl Alcohol (Methanol, Carbinol, Wood Alcohol, Columbian Spirit, Wood Spirit, Wood Naphtha, Methyl Hydroxide). Methyl alcohol is rarely found free in nature, but is often found in ester form (methyl salicylate) and in ether form (methoxyl group). Prior to 1923, methanol was obtained chiefly by the destructive distillation of wood, a method which now supplies only about 10 per cent of the total yearly production. The hydrogenation of carbon monoxide, carried out in the presence of zinc and chromium oxides under about 3,000 lbs. pressure at from 350 to 400° C., is the procedure most used now. Other alcohols (*n*-propyl and isobutyl) are also formed by this reaction and may be increased or decreased in amount by modifying the reaction condition.



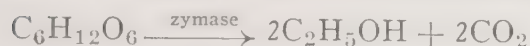
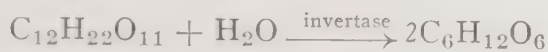
Methyl alcohol is a colorless liquid with a peculiar odor and a hot, sharp taste. It is miscible with ether, water and ethanol; its general solvent powers resemble those of ethyl alcohol. The vapors are irritating to the eyes, and, like ethanol, it burns easily.

The pharmaceutical use of methanol *per se* is prohibited, and under no conditions may it be used as a menstruum or solvent for medicinals. It may be used as a denaturant in ethyl alcohol which is employed for the preparation of solid extracts. However, in industry it is used extensively as a solvent and chemical agent.

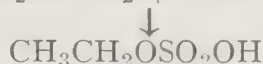
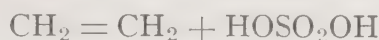
Ingestion of even small quantities of methanol produces a drunkenness similar to that of ethanol, a state which leads to eye injury, blindness and death. It is slowly oxidized to formic acid by the body.

Alcohol (Ethanol, Ethyl Alcohol, Spiritus Vini Rectificatus) U.S.P. (Methylcarbinol, Ethyl Hydroxide, Cologne Spirit, Wine Spirit). Ethanol has been known since earliest times as a fermentation product of

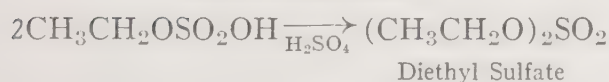
carbohydrates. An important source today is from the fermentation of molasses. The steps of the process are quite complicated,² but essentially they are:



A synthetic method of preparation using acetylene or ethylene has been employed, although only the ethylene procedure has shown commercial possibilities. Ethylene, $CH_2=CH_2$, plus one mole of water, H_2O , provides the essentials for a mole of alcohol. However, direct hydration of ethylene is difficult and gives low yields. By using sulfuric acid on ethylene to form ethylsulfuric acid and diethyl sulfate,

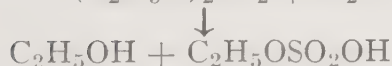
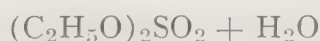
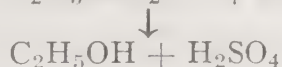


Ethyl Sulfuric Acid



Diethyl Sulfate

which are diluted with an equal volume of water, alcohol is formed and removed by distillation.



Alcohol of commerce is about 95 per cent by weight because this concentration of alcohol (95.5% w/w) and water (4.5% w/w) forms a constant-boiling mixture at 78.2° C. Pure alcohol boils at 78.3° C. and cannot be obtained by direct distillation.

Ethanol is a clear, colorless, volatile liquid having a burning taste and a characteristic odor. It is inflammable and miscible with water, ether, chloroform and most alcohols. Its chemical properties are characteristic of primary alcohols. Most incompatibilities associated with it are due to solubility characteristics. It does not dissolve most inor-

ganic and organic salts, gums, proteins, etc. Due to the aldehydes sometimes present in alcohol, the following chemical changes are often observed: the reduction of mercuric chloride to mercurous chloride, the formation of explosive mixtures with silver salts in the presence of nitric acid and the development of a dark color with alkalis.

Ethyl alcohol has a low narcotic potency. It is seldom used in medical practice as a therapeutic agent, but is almost always employed as a solvent, preservative, mild counterirritant or antiseptic. It may be injected near nerves and ganglia to alleviate pain or ingested as a source of food energy, for hypnotic effect, as a carminative or as a mild vasodilator. The body readily oxidizes ethanol, first to acetaldehyde and then to carbon dioxide and water.

Externally, it is a refrigerant, astringent, rubefacient, and slight anesthetic.

The specific uses of alcohol in pharmacy are extremely varied and numerous. Spirits are a class of pharmaceuticals using alcohol exclusively as the solvent, whereas elixirs are hydro-alcoholic preparations. Most fluid extracts contain a small percentage of alcohol as a preservative and solvent. In concentrations between 50 and 70 per cent, it is an efficient germicide, functioning by slow precipitation of the protoplasm in the bacterial cell.

OFFICIAL OCCURRENCE U.S.P.	PER CENT ALCOHOL
Diluted Alcohol	50.0

Dehydrated Alcohol (Dehydrated Ethanol, Absolute Alcohol) N.F. Absolute or dehydrated alcohol is ethyl hydroxide in a form as pure as it is possible to obtain.

There are many laboratory procedures available for the preparation of anhydrous ethanol. Some of the compounds used in these methods are calcium oxide, calcium sulfate, sodium sulfate, aluminum ethoxide, diethyl phthalate, diethyl succinate, etc. Commercially, absolute alcohol is prepared by azeotropic distillation of an ethanol and benzene mixture. Because the ethanol con-

tains about 5 per cent water, the resultant combination, ethyl alcohol-water-benzene, first distills at 64.8° C. (C_6H_6 74 per cent, H_2O 7.5 per cent and C_2H_5OH 18.5 per cent). All of the water is removed at this temperature, and then the remaining ethyl alcohol and benzene distill at 68.2° C. The ethyl alcohol is always in great excess; thus, when all the benzene has been removed, pure ethyl hydroxide is collected at 78.3° C.

Dehydrated alcohol has a great affinity for water and must be stored in tightly closed containers. It is used primarily as a chemical agent, but has been injected for the relief of pain in carcinoma and in other conditions where pain is local.

The Treasury Department of the U. S. Government oversees the use of alcohol and provides definitions and information pertaining thereto.*

"The term 'alcohol' means that substances known as ethyl alcohol, hydrated oxide of ethyl, or spirit of wine, from whatever source or whatever process produced, having a proof of 160 or more, and not including the substances commonly known as whisky, brandy, rum, or gin."

Besides alcohol available as ethyl alcohol, there are two other forms: (1) completely denatured alcohol and (2) specially denatured alcohol. Denatured alcohol is ethyl alcohol to which has been added such denaturing materials as render the alcohol unfit for use as an intoxicating beverage. It is free of tax and is solely for use in the arts and industries. There are two kinds:

1. Completely denatured alcohol is ethyl alcohol treated according to one of two formulas.

a. Contains alcohol, wood alcohol and benzene. This is not suitable even for external use.

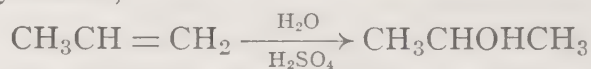
b. Contains alcohol, methanol, aldehyde and benzene. This one is usually used as an antifreeze.

2. Specially denatured alcohol is ethyl alcohol treated with one or more acceptable denaturants so that its use may be permitted for special purposes in the arts and industries. Examples are menthol in alcohol intended for use in dentifrices or mouth washes, iodine in alcohol intended for preparation of tincture of iodine; phenol, methyl salicylate or sucrose octa-acetate in alcohol intended for bathing or as an antiseptic and methanol in alcohol to be used in the preparation of solid drug extracts.

Isopropyl Alcohol³ (Propan-2-ol) N. N.R. (Petrohol). Isopropyl alcohol³ became recognized about 1935 as a suitable substitute for ethyl alcohol in many external uses, but it must not be taken internally. It is prepared, with Raney nickel as a catalyst, by the high pressure hydrogenation of acetone,



or, with sulfuric acid, from propylene by hydration,



Isopropyl alcohol is a colorless, clear, volatile liquid having a slightly bitter taste and a characteristic odor. It is miscible with water, ether and chloroform.

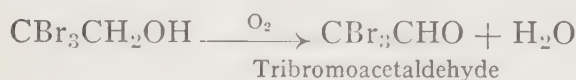
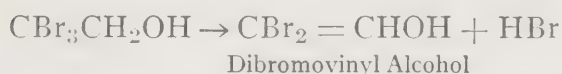
It is used to remove creosote from the skin and as a disinfectant for the skin and surgical instruments. A 40 per cent solution is approximately equal in antiseptic power to a 60 per cent solution of ethyl alcohol. In recent years it has been used in many toiletries and pharmaceuticals as a solvent and preservative. Isopropyl Alcohol Rubbing Compound N.F. is used to replace the rubbing compound of ethyl alcohol.⁴

Internally, isopropyl alcohol is oxidized and eliminated in much the same manner as is ethyl alcohol. However, it is about twice as toxic and may cause depression. Unlike methanol, no effects on the eye are noticed.

Amylene Hydrate (Tertiary Amyl Alcohol) U.S.P. (Dimethylethyl Carbinol). Amylene hydrate is a tertiary amyl alcohol, first used in 1894. It is synthesized from amylene by adding sulfuric acid and water

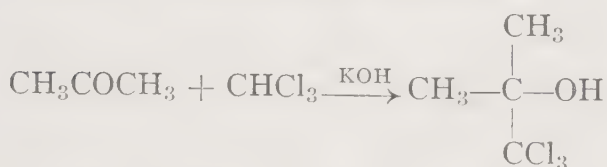
* Regulation No. 3, Industrial and Denatured Alcohol, published by U. S. Treasury Department 1927, 1938.

It is a white, crystalline material, soluble in water (3.5:100), alcohol or organic solvents. The drug usually is supplied in solution with amylene hydrate of such strength that 1 cc. of solution contains 1 gram of tribromoethanol. A distilled solution is prepared under specific directions which state that it must produce an orange-red color when tested with Congo red solution. If the color is blue or violet, decomposition of the drug has occurred. The decomposition products cause severe irritation, preventing the use of such a solution.



A freshly prepared solution is used rectally for basal anesthesia, but this use has decreased because of the fact that once a dose is administered none can be removed, and it is difficult to prevent an overdose.

Chlorobutanol U.S.P. (Chloretone, Acetonechloroform). Chlorobutanol is tertiary trichlorobutyl alcohol which may be synthesized from acetone and chloroform.



It is a white, crystalline solid having a characteristic camphorlike odor and taste. Because it readily volatilizes at room temperatures, chloretone is difficult to dry and must be stored carefully. The compound dissolves in water (1:125), alcohol (1:1), glycerin (1:10), all oils or in organic solvents.

It is widely used as a hypnotic and sedative, especially in motion sickness and whooping cough. The action and effectiveness are similar to chloral hydrate. As an antiseptic it is slightly better than phenol; a water solution is bacteriostatic and destroys *B. typhosus*. The germicidal properties are useful in preserving solutions of

alkaloids, synthetics and aqueous prescriptions for the nose and eye. In biologicals, it is extensively used to preserve glandular products and vitamins in capsules or liquids. There is also some local anesthetic action. Advantage is taken of this in making powders for topical use, oil sprays for nasal application and injectable solutions (Bismuth Subsalcylate Injection N.N.R. 3 per cent).

The average dose is 0.3 to 1.0 grams.

OFFICIAL OCCURRENCE	PER CENT CHLOROBUTANOL
N.F.	
Ephedrine Sulfate Solution...	0.5

Brometone (Tribromotertiary Butyl Alcohol). Brometone, the bromine analogue of chlorobutanol, is prepared from bromoform and acetone. It has some use as a sedative and a hypnotic and is similar in action to bromides, but it does not cause bromidism.

The average dose is 0.3 Gm.

Iothion (Iopropane, Di-iodoisopropyl Alcohol). Iothion ($\text{CH}_2\text{ICH}_2\text{OHCH}_2\text{I}$) is an organic iodide developed for the external administration of iodine. It is readily soluble in oils or organic solvents. Absorption through the skin is rapid and it exerts the effects of the iodide ion.⁵

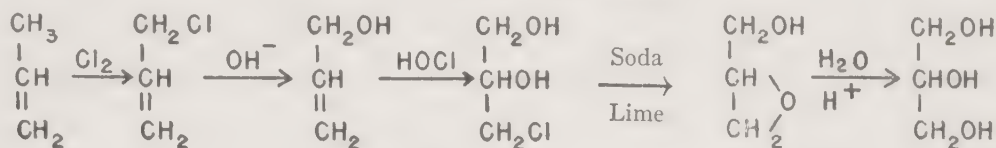
DIHYDRIC ALCOHOLS (GLYCOLS)

Glycols⁶ are alcohols with two hydroxyl groups in the molecule. The lower molecular weight glycols are colorless, somewhat hygroscopic liquids. They have solubility properties between those of water and of hydrocarbons, i.e., they are miscible with water yet will dissolve volatile oils, some dyes, resins and a few gums. Toxicity studies on the glycols⁷ indicate that they vary according to the number of carbon atoms and the position of the hydroxyls and that their derivatives also vary with the substituent. They resemble the monohydric alcohols in chemical properties.

The glycols can be prepared, with potassium acetate and subsequent hydrolysis, from an olefin or by oxidation with potassium permanganate.

Ethylene Glycol (Glycol, Ethanediol-1,2). Ethylene glycol, the simplest stable member of the dihydric series, is not used in pharmacy. When ingested, it is oxidized to poisonous oxalic acid. A major commercial use of ethylene glycol is as an antifreeze for liquid-cooled motors.

triol, Trihydroxypropane). Glycerin, an important pharmaceutical for many years, was isolated in 1779; its structure was determined in 1835. For over a hundred years, the principal source of glycerin was the hydrolysis of fats (q.v.). In 1938 a method was devised to produce glycerin from propylene, a petroleum product:



Propylene Glycol N.F. (Methylethylene Glycol). Propylene Glycol ($\text{CH}_3\text{CHOHC}-\text{H}_2\text{OH}$) is a clear, viscous, nontoxic liquid similar to glycol. In properties, it is typical of the series. It is miscible with water or organic solvents. Although it will dissolve volatile oils, it is immiscible with fixed oils. As a replacement for glycerin it is used as a solvent in pharmaceuticals, perfumes and flavoring extracts. It is nontoxic on internal administration and has a strong bactericidal activity. A recent use is the sterilization of air in hospitals and office buildings by vaporization in the air.

Diethylene Glycol ($\text{HOCH}_2\text{CH}_2\text{OCH}_2-\text{CH}_2\text{OH}$) is a very useful solvent in industry, but is seldom used for pharmaceuticals. It has properties similar to those of ethylene glycol and is extensively used as an antifreeze. This glycol was used in 1937 as a solvent for an elixir of sulfanilamide and was the cause of many deaths.⁸

2-Ethyl-Hexandiol-1,3 [$\text{CH}_2\text{OHCH}(\text{C}_2\text{H}_5)\text{CHOHCH}_2\text{CH}_2\text{CH}_3$] is a viscous, clear liquid similar in physical properties to glycerin. It is nonirritating to the skin, mucous membranes or eyes, and is an effective insect repellent, particularly for mosquitoes. Several insect repellent preparations now available contain this glycol.

TRIHYDRIC ALCOHOLS

Glycerin (Glycerol) U.S.P. (Propane-

A fermentation process has also been used for the production of glycerol by a method similar to that employed for ethyl alcohol. The reduction of acetaldehyde is inhibited by the use of sodium bisulfite or sodium carbonate. The glyceraldehyde, an intermediate, is then converted into glycerol.

Glycerin is a clear, colorless, viscous liquid with a faint odor and a sweet taste. It is highly hygroscopic and is miscible with alcohol or water but insoluble in organic solvents. The chemical properties are closely allied with those of alcohols. By strong heating or treatment with dehydrating agents, it yields acrolein. Glycerin combines with boric acid or borates to produce a stronger acid solution than boric acid and thus is incompatible with carbonates or other materials sensitive to acid. Most oxidizing agents react to form oxalic acid and carbon dioxide.

The applications of glycerin in pharmacy are extremely varied and its uses in industry alone would require a book⁹ for complete discussion. In the classes of preparations known as glycerites and fluidglycerites, it is employed as a vehicle. The solvent and preservative properties of glycerin are widely used, while the consistency and sweet taste make it suitable for use in cough remedies. As an emollient and demulcent it is an ingredient in lotions and hand creams. An irritant property, perhaps due to dehydration, is made use of in glycerin suppositories, which stimulate bowel movements. In prescription com-

pounding it is frequently used as a stabilizer, to retard precipitation by decreasing ionization in many cases, and as a softening agent.

GLYCEROPHOSPHATES

Glycerophosphates of metals such as sodium (N.F.), calcium (N.F.), manganese (N.F.), iron (N.F.) and potassium were introduced many years ago as tonics. The theory was that a metal in combination with glycerophosphoric acid should be more readily assimilated than would be a mineral acid salt. Since lecithin contains glycerophosphate in its molecule and is present in all cells of the body, perhaps elements essential for growth might be advantageously administered as glycerophosphates. Also glucose metabolism, thought to produce some glycerophosphoric acid which is eventually hydrolyzed to glycerol and phosphoric acid, adds strength to the possible value of these salts. The therapeutic usefulness, however, of glycerophosphates is now very much doubted, and they are used only in some proprietary "tonics."

POLYHYDRIC ALCOHOLS

Erythritol (Tetrahydroxybutane, Erythrol, Erythrite). Erythritol is a tetrahydric alcohol having two asymmetric carbon atoms. Because of these, it exists in two optically active forms, *d* and *l*, and a meso form (an internally compensated form). Only the mesoerythritol is found in nature. The free alcohol is found in the alga *Proto-coccus vulgaris* and as the ester of orsellinic acid in some lichens. The *d* and *l* forms may be prepared synthetically, the *l* form by re-

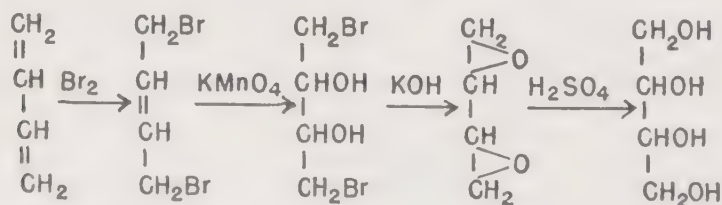
In the form of erythritol tetranitrate it is a useful vasodilator for arterial hypertension (q.v.).

***d*-Mannitol** N.N.R. (Mannite, Hexit). *d*-Mannitol $[\text{CH}_2\text{OH}(\text{CH}_2\text{OH})_4\text{CH}_2\text{OH}]$ occurs in nature as the chief constituent of manna and is also present in a host of other plants. It may be prepared by the reduction of mannose or fructose. This sweet-tasting alcohol appears as white, odorless crystals, soluble in water, slightly soluble in alcohol, and insoluble in organic solvents.

Mannitol is now being used to measure glomerular filtration in the kidney since it is filtered at the glomeruli and is not reabsorbed but remains in the urine. Mannitol Hexanitrate is in the N.N.R.

***d*-Sorbitol** (Sionon) is found in a number of fruits and berries and is readily prepared by the hydrogenation of glucose. Sorbitol is a white powder. It is also available commercially as "Alex," a noncrystallizable liquid containing 83 per cent sorbitol. This form is used in cosmetics and galenicals. *d*-Sorbitol is isomeric with mannitol and has similar properties. However, it is metabolized by the body as a source of food; mannitol is not. An outstanding property of sorbitol is its narrow humectant range. It serves as a starting material for the synthesis of vitamin C and its solutions are widely used in industry and in pharmaceutical manufacturing. It has advantages over glycerin for many purposes.

Dulcitol can be obtained from manna produced in Madagascar. Some other plants also contain it, but it is readily produced by the reduction of galactose.



duction of *d*-threose and the racemic form from butadiene.

Erythritol has a sweet taste, ready solubility in water and insolubility in alcohol.

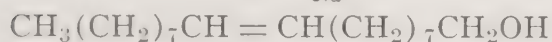
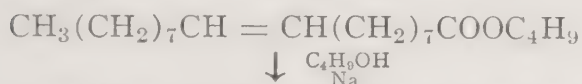
UNSATURATED ALCOHOLS

Oleyl Alcohol N.F. Oleyl alcohol $[\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_2\text{OH}]$

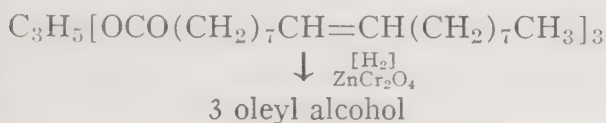
is "a mixture of aliphatic alcohols consisting chiefly of



It is prepared by the Bouveault-Blanc method of reduction on butyl oleate,



or by the hydrogenation of triolein in the presence of zinc chromite.



The alcohol exists as a pale yellow liquid having a faint characteristic odor and bland taste. It is soluble in alcohol, in fixed oils or in mineral oil.

It is a useful emulsifying assistant and not an emulsifying agent because the hydroxyl group is sufficiently polar to be oriented to-

ward the aqueous phase in emulsions, while, in the fat phase, the aliphatic chain remains dissolved.

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7

Aliphatic Ethers

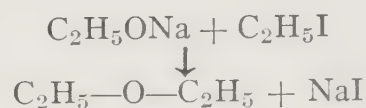
Ethers, or organic oxides, are characterized by the structure $R-O-R$ and may be considered as derivatives of water ($H-O-H$) which has had the hydrogen atoms replaced by the same or different chemical groups, such as alkyl, aryl, alicyclic or heterocyclic. Inasmuch as ethers are usually prepared from alcohols, they are more often considered as derivatives of alcohols ($R-O-H$) in which the hydrogen has been replaced by one of the previously mentioned groups. Less often, they are thought of as a hydrocarbon with a hydrogen replaced by an alkoxyl group ($R-O-$), or as isosters of hydrocarbons, where a methylene group ($-CH_2-$) is replaced by an oxygen atom.

An ether in which the groups R of $R-O-R$ are the same is known as a simple ether; when the R 's differ, it is a mixed or unsymmetrical ether.

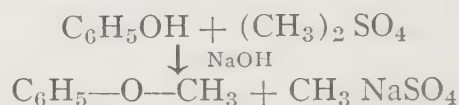
PREPARATION

Preparation of ethers can be accomplished by any one of several procedures. The two most common and useful are the Williamson synthesis and the sulfuric acid method.

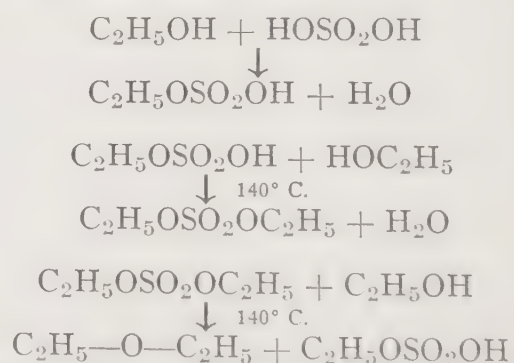
Williamson's synthesis is applicable for the preparation of either simple or mixed ethers. It requires the reaction between an alkyl halide and a sodium alkoxide.



An adaptation of this method is used to form alkoxyl derivatives of phenols, using $NaOH$ and methylsulfate or ethylsulfate.



The sulfuric acid method is particularly suitable for the preparation of ethyl ether from ethanol and for the preparation of other simple ethers from primary alcohols such as methyl to isoamyl. Secondary and tertiary alcohols are unsuited to the procedure, as they are easily dehydrated to alkenes by the sulfuric acid. The following reactions represent the steps in the formation of ethyl ether from ethanol:



Once the reaction is started, alcohol is added at the same rate that the ether distills off, and

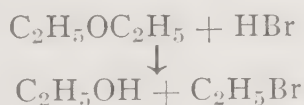
the water formed is retained by the sulfuric acid. The process is continuous until the acid becomes too dilute. The name "sulfuric ether" has thus resulted. Ether so produced has the possibility of being contaminated by thioacids, thioethers, sulfates, sulfur oxides, ethylene, aldehydes, organic acids and alcohol.

CHEMICAL PROPERTIES

Except for the saturated hydrocarbons, ethers are perhaps the most chemically inert class of organic compounds. They react neither with sodium, strong acids or bases at moderate temperatures nor with phosphorous trichloride, cold phosphorous pentachloride, alkali metals or oxidizing agents.

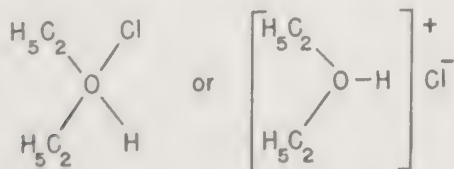
Potassium dichromate in concentrated sulfuric acid, when warmed, will react with ether to produce successively acetaldehyde, acetic acid, carbon dioxide and water. The reaction may be used as a basis for quantitative assay.

At low temperatures, ethers combine with strong mineral acids to form oxonium salts, which usually are unstable at moderate temperatures.* However, the linkage can be split with strong hydrobromic or hydriodic acid.



The hydrogens of the ethers are readily attacked by bromine and chlorine to form halogenated ethers. Because of the stability of ethers, they are most useful as

* The structure of oxonium salts may be shown by using ethyl ether and hydrochloric acid.



This reaction is used to distinguish ethers from hydrocarbons. In some cases, the oxonium salts are stable above room temperature. Dioxane, as an example, forms an oxonium compound with sulfuric acid; the oxonium compound has a melting point of 101° C.

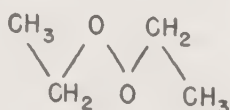
solvents; this is particularly true of diethyl ether.

The ethers are more volatile than the isomeric alcohols and they decrease in volatility, inflammability and water solubility as the molecular weight increases. All organic solvents are miscible with ethers, as are fixed and volatile oils.

Diethyl Ether (Sulfuric Ether, Ethoxyethane). Diethyl ether ($\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$), usually referred to as "ether," has been known for more than four hundred years and its structure has been known since 1807. It is readily prepared (q.v.) and occurs as a volatile, inflammable liquid, colorless, lighter than water, slightly soluble in water, and having a characteristic odor. By reason of its close chemical relationship to the hydrocarbons, it has become a most useful solvent. The molecular weight of oxygen is 16 and that of a methylene group is 14, thereby allowing the comparison of diethyl ether, b.p. 34.6° C., with *n*-pentane, b.p. 36.1° C. Ether boils at a much lower temperature than does the corresponding ethyl alcohol, b.p. 78.5°. This difference is due to hydrogen bonding in the alcohol and of the unassociated form, in the case of alkanes and ethers. The solvent powers of ether are very great for most organic compounds, for example, alkaloids, fats, amines, sterols, waxes, etc., that do not contain a large number of hydroxyl groups (carbohydrates). Most inorganic complexes or salts are insoluble in ether, but it does dissolve the halogens and mercuric chloride. The low boiling point of ether makes it first choice as an extraction solvent when subsequent evaporation or distillation is necessary. Few substances are injured by heating at this low temperature.

Although ether is immiscible with water, each solvent does dissolve some of the other. At room temperature, ether dissolves about 1 to 1.5 per cent of water and water dissolves about 8 per cent of ether. Ether may be dried in several ways, but first the peroxides and alcohol should be removed by extraction with water. The wet ether is then treated for

several days with a drying agent such as calcium chloride, after which it is decanted into a clean container, and solid sodium or sodium hydroxide is added. It may be decanted and used, or it may be redistilled. In laboratory operations, ether is a dangerous chemical because it is highly inflammable, forms explosive mixtures with air and has a low flash point. It is two-and-one-half times heavier than air and thus settles in low places. Upon long standing in contact with air (partially-filled containers), ether is known to develop peroxides. Their development is favored by ultra-violet light and sunlight. In well-filled containers, either glass or tin-plated iron, the peroxides will form in about six months and remain for about one year. It appears that in old ether (over two years), the content of peroxides decreases and aldehydes are formed from the alcohol present. These peroxides are nonvolatile and remain as a residue when such an ether is evaporated. In such cases, they explode with terrific force when heated to about 100° C. and constitute a real danger. The peroxides are not only found in ethyl ether, but also are possible in methyl, isopropyl and butyl ethers.



Ether that is old (more than six months) or suspected of containing peroxides, may have them destroyed by shaking the ether with an aqueous solution of a reducing agent such as ferrous sulfate, zinc dust and sulfuric acid, sodium sulfite, ferrous chloride, sodium hydrosulfite, cathechol, etc., or by filtering through activated alumina. Ether supplied in glass bottles contains iron wire to prevent peroxide formation. Many studies have been made to find a preservative for ether, and the best one found involves keeping ether in copper or copper-plated containers. Mercury, too, has been found to be a satisfactory stabilizer since, like iron and copper, it is preferentially oxidized. Acetaldehyde stems from

the alcohol present and results in the formation of organic acids.

Dimethyl ether is a simple ether introduced as an anesthetic in 1867. Since it is a gas and a high concentration is necessary for effectiveness, it has never gained favor.

Ether (Ethyl Ether, Diethyl Ether) U.S.P. Faraday is credited with first observing (in 1815) the depressant property of ether; it was used in surgical anesthesia in 1842 by Long and in 1846 by Morton.¹ Its preparation and properties have been discussed previously. It occurs as a colorless, mobile liquid having a burning, sweetish taste and a characteristic odor. Ether U.S.P. is intended for anesthetic use and thus has some rigid specifications as to content and method of handling. It may contain up to 4 per cent of alcohol and water. The alcohol has little value as a preservative but does raise the boiling point and prevent frosting on the anesthetic mask. In the U.S.P., a caution limits the size of container to 3 kilos and permits the ether to be used only up to 24 hours after the container has been opened.

The ether must be free of acids, aldehydes and peroxides. Acids are tested for by using moist litmus paper or .02N sodium hydroxide. A test for aldehydes, sensitive to 1 part in 1,000,000, using Nessler's solution (alkaline mercuric potassium iodide T.S.) shows no yellow color when the test is negative. The peroxide test is carried out on 10 cc. of ether. One cubic centimeter of potassium iodide T.S. is added and the mixture is shaken for one hour (compare with Ethyl Oxide U.S.P.). If peroxides are present, the potassium iodide, as a reducing agent, has its iodide ion oxidized to free elemental iodine (colored).

Ethyl Oxide (Solvent Ether) U.S.P. This is similar in every respect to Ether U.S.P. except that it is not required to be of such high purity and, therefore, may be produced more cheaply. The amounts of aldehydes and peroxides may be greater. The official caution is that it is not to be used

for anesthesia. Potassium hydroxide is used in the test for aldehydes and is sensitive² only to about 5 parts in 10,000.

The test for peroxides is chemically the same. A solution of potassium iodide is used and the period of shaking is reduced from one hour to one minute. This, of course, allows some peroxide to be present in ethyl oxide.

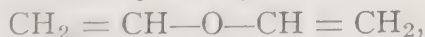
It is employed as a solvent (q.v.) and in pharmaceuticals. Locally, ethyl oxide is strongly irritant, but it has been used orally for nausea and flatulent colic.

OFFICIAL OCCURRENCE	PER CENT ETHYL OXIDE
U.S.P.	
Apsidium Oleoresin	...
Collodion	75.0
Flexible Collodion	...
N.F.	
Ether Spirit	32.5
Compound Ether Spirit.....	32.5
Ethereal Oil	50.0
Salicylic Collodion	75.0

Ethyl *n*-Propyl Ether ($C_2H_5OCH_2CH_2CH_3$) is a mixed, or unsymmetrical, ether. It may be prepared by the Williamson synthesis. It is a colorless liquid having a boiling point of 63.6° C. In odor it resembles ethyl ether and is similar in chemical and physical properties, requiring copper to prevent peroxide formation. It is one and one half to two times as effective for anesthesia as ether.

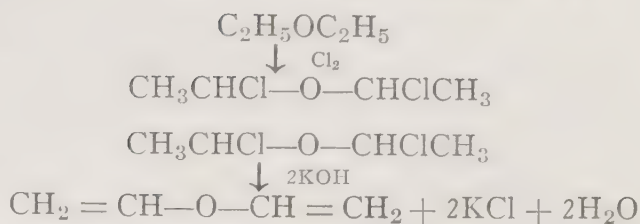
Isopropyl ether and *n*-butyl ether are known, but are of value only as solvents.

Vinyl Ether (Divinyl oxide) U.S.P. (Vinethene). Vinyl ether was introduced in 1930 as an anesthetic agent. Since unsaturation is known to enhance anesthetic action, e.g., ethylene-ethane. Leake and Chen³ studied a series of unsaturated ethers and found that divinyl ether,



the lowest member of the unsaturated series of ethers, was the most potent and the least toxic.

The usual methods of synthesis were unsatisfactory, but, in 1931, Ruigh and Major⁴ published a synthesis.



This method has several complications which cause a low yield and the formation of contaminants such as acetylene, hydrogen, chloroethyl vinyl ethers, ethylene peroxides, dioxane and aldehydes. A purification process is necessary to purify the unsaturated ether for use in anesthesia.

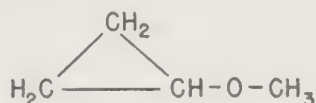
Vinyl ether is a clear, colorless liquid having a characteristic ethereal sweet odor. There is generally present an antioxidant, 0.01 per cent of phenyl- α -naphthylamine, producing a slight purple fluorescence. It is miscible with organic solvents and slightly soluble in water (4 per cent). It burns and forms explosive mixtures with air. The double bonds of vinyl ether cause a lower boiling point than its saturated analogue, ethyl ether. Perhaps because of the unsaturation, vinyl ether is not as stable as ethyl ether. It is readily oxidized by air to formaldehyde, formic acid, acetic acid and peroxides. A caution is given in the U.S.P., limiting containers to 200 cc. and restricting use to within 24 hours after opening. The presence of alkalies helps prevent decomposition, and phenyl- α -naphthylamine, a nonvolatile organic base, has been found satisfactory. The U.S.P. has a limit on nonvolatile matter, matter which may be due to the stabilizing amine and resin formed by polymerization of the vinyl ether. Acids and bases may be detected by shaking the ether with water and testing with litmus paper. The water should be neutral, but if the organic amine (q.v.) is used as a preservative, the water will be alkaline.

Commercial divinyl ether supplied for anesthesia contains about 4 per cent alcohol to reduce volatility and to keep water vapor from freezing on the anesthetic mask. This might occur because of water vapor in the breath and the low temperature caused by the rapid evaporation of vinyl ether.

Vinyl ether is about seven times more active as a general anesthetic than is ethyl ether. It is used much the same as is diethyl ether for anesthesia, but is more rapid and more toxic, requires lower blood concentration, has a prompt recovery and few side-reactions. Primary application is made of it in minor surgical operations of short duration.

Several other unsaturated ethers, for example, allyl methyl ether and isopropenyl methyl ether, have been studied; all are too toxic.

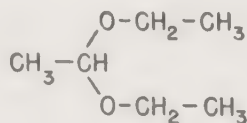
Cyclopropyl Methyl Ether⁵ (Cyprome Ether) is a combination of a strong anesthetic compound, cyclopropane, in an ether type of structure.



It is a more potent anesthetic than ethyl ether and is similar in physical and chemical properties.

Cyclopropyl Ethyl Ether (Cypreth) is the next compound in the homologous series and possesses the same characteristics as cyprome. It, along with the propyl and butyl derivatives, shows that as molecular weight increases, so does the potency, but that volatility and inflammability decrease. Both cyprome and cypreth have been used on man.

Acetals (Double Ethers). Diethyl acetal is a simple acetal prepared from acetaldehyde and ethyl alcohol. It is a colorless liquid, soluble in water (1:18), very soluble in organic solvents and boiling at 104° C.



Acetals are more reactive than ethers, being stable with alkalis but decomposed with acids.

Diethyl acetal is not suitable for inhalation anesthesia. It is, however, a good hypnotic and has been used in veterinary medicine.

Related structures, such as alkene oxides and the heterocyclic structures, furan and dioxane, do not possess anesthetic properties. Ethylene oxide and propylene oxide are two that have been studied.

PHYSIOLOGIC ACTION AND PROPERTIES

In the saturated and unsaturated series of simple and of mixed ethers the potency and toxicity, as well as the boiling point, increase with the molecular weight. Dimethyl ether was once introduced into medicine, and ethyl *n*-propyl ether is reported to be safe for man. A study of an aliphatic series indicates that the potency varies inversely with the boiling point. Ethers composed of branched chains are usually more potent and have a lower boiling point than their straight chain isomers. Just as the unsaturated hydrocarbons, e.g., ethylene and propylene, are more potent than the corresponding saturated hydrocarbon, so is it with the unsaturated ethers. In general, the unsaturated ethers are more volatile, less stable and more potent than their saturated counterparts.

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8

Aliphatic and Alicyclic Aldehydes and Ketones

GENERAL CONSIDERATIONS

Aldehydes and ketones are characterized

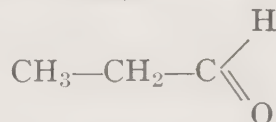
by the carbonyl group, $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$. This, of course, is equivalent to $-\text{C}(\text{OH})_2-$, in which form it may sometimes exist in the presence of water. The aldehydes have a hydrogen atom attached to this carbonyl to give

$\begin{array}{c} \text{H} \\ | \\ -\text{C} = \text{O} \end{array}$, which is called the aldehyde group. In ketones the valence bonds are attached to carbon, and we get compounds of

the general structure $\begin{array}{c} \text{O} \\ || \\ \text{R}-\text{C}-\text{R}' \end{array}$. In alicyclic ketones the carbonyl group may be contained in the ring; whereas in alicyclic aldehydes the carbon of the aldehyde group must be on the end of a chain and, therefore, can only be a substituent for hydrogen of the nucleus or side chain.

The nomenclature of these compounds follows any one of several systems. The aldehydes may be regarded as derivatives of the corresponding primary alcohols or of the acids to which they will oxidize, or they may be looked upon as substitution products of acetaldehyde. In addition, the names may

follow the rules that have evolved from the Geneva system. Thus,



is propyl aldehyde, propionaldehyde, methylacetaldehyde or propanal. In more complicated compounds, the aldehyde group may be considered as a substituting one and given the prefix formyl- or the suffix -carboxaldehyde; the substance given as an example would be formylethane or ethanecarboxaldehyde. Ketones are named according to the radicals, as substitution products of acetone or systematically using the suffix -one or the prefixes oxo- or keto-.

Thus, $\begin{array}{c} \text{O} \\ || \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3 \end{array}$ is ethyl propyl ketone, ethylmethylacetone, hexan-3-one, 3-hexanone, hexanone-3 or 3-ketohexane.

Very few aldehydes exist as such in nature because the characteristic group is easily converted to the carboxyl of acids by oxidation. On the other hand, ketones are rather resistant to oxidation because this can only take place by disrupting the molecule. They are also rather stable in other ways and frequently are found in natural materials,

TABLE 10. PHYSICAL CONSTANTS OF CERTAIN COMMON ALDEHYDES AND KETONES.

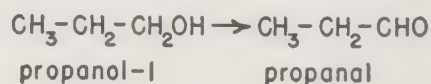
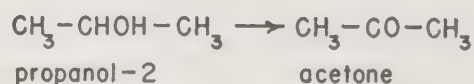
COMPOUND	BOILING POINT	SPECIFIC GRAVITY (20° C.)	SOLUBILITY (WATER AT 20° C.)
Formaldehyde	-21.0		sol.
Acetaldehyde	20.8	0.792	misc.
Propanal	48.8	0.797	1:5
Butanal	73-74	0.805	1:15
Pentanal	102-103	0.809	slight
Hexanal	116-118	0.834	insol.
Octanal	170	0.821	insol.
Decanal	209		insol.
Citral	226-228	0.887	insol.
Citronellal	204-208	0.856	insol.
Acetone	56.5	0.790	misc.
Diacetyl	88.0	0.993	1:4
Diethyl ketone	101.5	0.816	1:25
Ethyl methyl ketone....	79.6	0.805	1:4
Methyl propyl ketone....	102.0	0.809	insol.
Dipropyl ketone	144.0	0.825	insol.
Amyl methyl ketone....	151.0	0.828	insol.
Amyl ethyl ketone	170.0	0.857	insol.
Hexyl methyl ketone....	172-173	0.820	insol.
Methylheptenone	173.4	0.855	insol.
Cyclohexanone	154-156	0.945	insol.

especially in volatile oils. Both aldehydes and ketones can be prepared readily and, if the former are protected from oxidation and reagents, are permanent enough to be useful in therapy and in synthetic procedures.

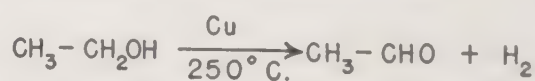
The aliphatic aldehydes with low molecular weight are colorless, neutral gases or liquids with a characteristically pungent odor and are more or less soluble in water, but the higher ones may be solid, odorless and insoluble. The ketones are liquids or solids with pleasant odors usually, and only those with low molecular weight are soluble in water. Most of the common alicyclic compounds are similar to these in physical properties, but they are almost entirely derivatives of terpenes and will be considered in a later chapter. The constants of some common aldehydes and ketones are given in Table 10.

PREPARATION

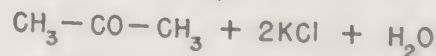
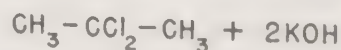
Aldehydes and ketones are generally made by very similar processes. As has already been noted, this can be accomplished easily by oxidation of primary and secondary alcohols, although it is not often easy to prevent further oxidation of the aldehyde to the acid.



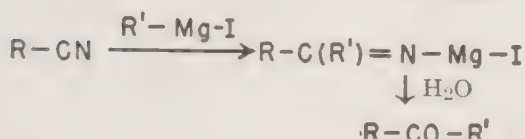
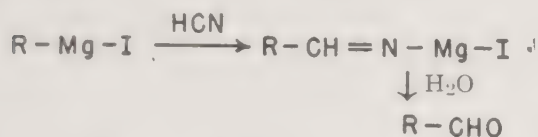
A still better process is direct dehydrogenation by passing the vapors of the alcohol over metallic copper at about 250° C.; this gives excellent yields for formaldehyde, acetaldehyde, acetone and cyclohexanone.



Another method is to hydrolyze dihalogen compounds in which the two halogen atoms are connected to the same carbon atom. For example, formaldehyde can be made from methylene iodide and acetone from 2,2-dichloropropane.

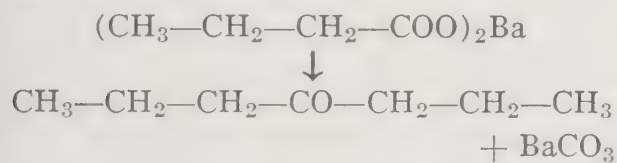


Addition of the Grignard reagent to formic esters or to hydrogen cyanide and subsequent hydrolysis will give aldehydes, while ketones are obtained in a similar way by using amides or nitriles.



This is especially convenient for those compounds having a high molecular weight.

For simple, volatile ketones one of the most practical methods is to distill a salt of barium, calcium or thorium. This can be illustrated by the preparation of dipropyl ketone from barium butyrate.



If an aldehyde is to be made in the analogous way, the salt must be mixed with a formate, and the product will always be contaminated with a ketone. Thus, a mixture of barium butyrate and barium formate will give dipropyl ketone, as already noted, as well as the desired butyric aldehyde.

Aldehydes often can be made by reduction of acid derivatives, using hydrogen with a catalyst such as palladium. Under other con-

ditions of reduction, it is usually difficult to prevent further change to primary alcohol.

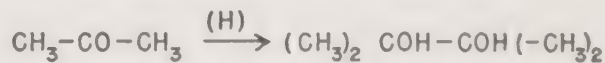
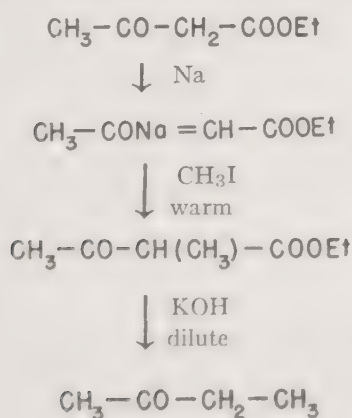
Finally, ketones frequently can be prepared with advantage from substituted acetoacetic ester by appropriately conducted hydrolysis with dilute acid or alkali. The reactions for producing ethyl methyl ketone from acetoacetic ester will illustrate. (See bottom of preceding column.)

CHEMICAL PROPERTIES

Aldehydes easily can be oxidized to the corresponding acids, as has already been noted. Reagents such as Fehling's solution and ammoniacal silver nitrate are reduced quite readily when warm; even oxygen of the air can bring about a gradual change, so that caution must be exercised in preserving them. The ketones are much more stable under the same conditions; they can only be oxidized by disrupting the molecule.

The carbonyl group has great capacity for adding any one of a variety of reagents, in the majority of cases to form a hydroxyl group.

1. Hydrogen can be added to reduce the compound to an alcohol. This reduction can be accomplished by sodium amalgam, by zinc and acid, by hydrogen and a catalyst, electrolytically, and by other means. Very frequently, especially with ketones, the simple alcohol is accompanied by other products such as glycols. Thus, the reduction of acetone gives, in addition to isopropyl alcohol which is the chief product, some of a glycol which is known as pinacone or pinacol.



The amount of pinacone that is produced may be greatly increased, or it may even be made the main product, by using magnesium amalgam as the agent under anhydrous conditions.

2. Ammonia adds to some of the lower aldehydes to give compounds of the type R—CHOH—NH_2 , which are crystalline and soluble in water. Because the reaction can

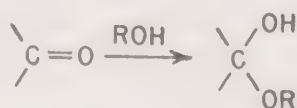
be largely reversed by acids, a convenient method of isolation and purification, the addition product is often called an "aldehyde ammonia." However, there is a great tendency toward decomposition to form complex compounds. Ketones do not usually add ammonia, except at low temperatures, but they condense with it as they do with amines.

3. Hydrogen cyanide adds to form hydroxynitriles or cyanohydrins; $R-CHOH-CN$ is formed from aldehydes, $R_2COH-CN$ from ketones. The reaction may be stopped or reversed by alkalis. The cyanohydrins are useful intermediates in synthesis because the $-CN$ group can be hydrolyzed to a carboxyl group.

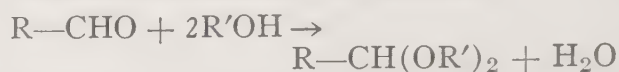
4. Sodium bisulfite reacts with aldehydes to form compounds of the formula $R-CHOH-SO_3Na$. These are crystalline and more or less soluble in water, but they usually can be separated if the salt is used in saturated solution and particularly if the aldehyde is dissolved previously in an anhydrous solvent such as ether. The reaction is easily reversible by acids or alkalis, which makes a convenient method of isolation and purification. The same reactions can be performed with aliphatic methyl ketones, such as acetone, and with some alicyclic compounds, such as carvone (q.v.).

The Schiff test for the presence of aldehydes may depend initially upon a similar reaction. The reagent is prepared by decolorizing fuchsin with sulfur dioxide. When a small amount of aldehyde is added, a red or purple-red color is produced; this color is more or less easily removed by acids, but not in the case of formaldehyde. Ketones do not give this test.

5. Water undoubtedly adds to the carbonyl group to produce hydrates, but these are seldom stable enough to isolate, except under special circumstances. Analogously, alcohols could be expected to add, forming hemiacetals.

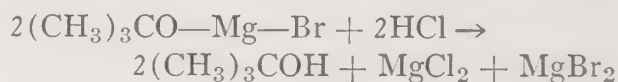
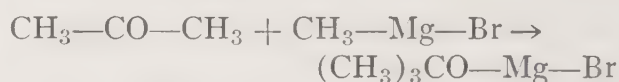


The reaction is highly reversible, and, while such compounds usually are very unstable, they can be isolated in some cases (chloral alcoholate). The principle of hemiacetal formation is undoubtedly involved in the cyclization of monosaccharides. In the presence of a trace of acid, however, aldehydes condense with alcohols to form acetals.



These can be hydrolyzed to aldehydes by boiling with acids and are, therefore, sometimes very useful.

6. The Grignard reagent will add to either aldehydes or ketones, and the resulting products can be hydrolyzed to alcohols. By this convenient method almost any desired alcohol can be synthesized; from formaldehyde a primary, from other aldehydes a secondary and from ketones a tertiary alcohol is formed. For example, acetone and methyl magnesium bromide could be used to prepare tertiary butyl alcohol.



7. When acetaldehyde is treated with a dilute alkali, an addition takes place to produce the compound $CH_3-CHOH-CH_2-CHO$. The mechanism of the reaction is rather complex, but the final product is as if there were simple addition of one molecule to the carbonyl group of another. The compound is called aldol because it is both alcohol and aldehyde, and the process is known as aldol condensation. Aldol, which is a colorless, heavy liquid, can be distilled under reduced pressure, but is partly decomposed to acetaldehyde, and also largely to crotonaldehyde by dehydration. Other aldehydes of the series will undergo a similar polymerization, but not if they contain no alpha hydrogen, such as in trimethylacetaldehyde, $(CH_3)_3C-CHO$.

When typical lower aldehydes of the aliphatic series are boiled with alkalis, they form insoluble, orange or brown resins. This

reaction, which serves to distinguish them from formaldehyde and aldehydes of the aromatic and heterocyclic groups, is probably a further aldol condensation.

Ketones also sometimes give a reaction that is similar in end-product to aldol condensation. For example, acetone with solid barium hydroxide at 0° C. produces diacetone alcohol,



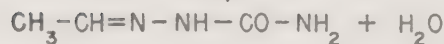
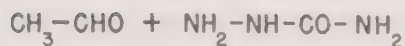
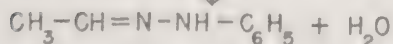
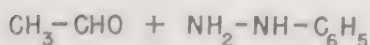
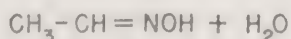
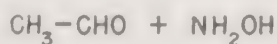
a liquid boiling at 164° C. It easily loses water to form mesityl oxide,



In no instances do ketones resinify as do aldehydes.

8. On standing or in the presence of catalysts, aliphatic aldehydes, but not ketones, polymerize in quite another way. Acetaldehyde with a small amount of acid is converted to a trimer, $(\text{CH}_3-\text{CHO})_3$, known as paraldehyde. If this is heated with sulfuric acid, the process is reversed. On the other hand, if the original reaction is conducted at temperatures below 0° C., there is produced a solid substance that is known as metaldehyde, probably a tetramer, $(\text{CH}_3-\text{CHO})_4$. This also can be reconverted to acetaldehyde by warming with acids. Neither of these polymers shows any of the typical reactions of carbonyl compounds, nor do similar products from other aldehydes, and the structure is essentially that of acetals (see paraldehyde).

Either aldehydes or ketones condense with substances containing active hydrogen, such as were found in the formation of acetals from alcohols. One common reaction of this type is with primary amines such as hydroxylamine, phenylhydrazine or semicarbazide. In all cases there is probably a primary addition at the carbonyl group, but water is eventually split out, as illustrated using acetaldehyde.



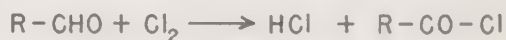
The products are called oximes (acetaldoxime), phenylhydrazones (acetaldehyde phenylhydrazone) and semicarbazones (acetaldehyde semicarbazone), respectively. In most cases these are crystalline substances with well-defined melting points and serve to identify specific aldehydes or ketones.

When phosphorus pentachloride is triturated or warmed with aldehydes or ketones, the carbonyl oxygen is converted to two chlorine atoms.

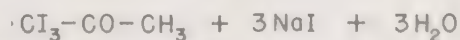
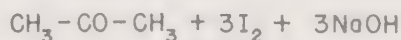


This is perfectly analogous to the action of phosphorus pentachloride on an alcohol, where an $-\text{OH}$ group is displaced by a chlorine atom, since the carbonyl oxygen is equivalent to two hydroxyl groups.

Halogens have no effect upon the carbonyl group in general, but may substitute for hydrogen in surrounding alkyls, just as they do in paraffin hydrocarbons. Dry chlorine, however, may act on the hydrogen of the aldehyde group to produce an acyl chloride.



If the aldehyde or ketone has a methyl group connected to the carbonyl, as in acetaldehyde and methyl alkyl ketones, halogens in the presence of dilute alkalis will convert it to a haloform. Ethyl alcohol, which can be oxidized by the hypohalite, will also give this haloform reaction. The action of iodine and sodium hydroxide on acetone to form iodoform will illustrate.



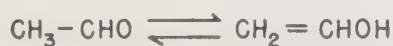
The ease with which the halogenation is brought about would suggest that it is really addition to the double bond of an enol form

(see below) instead of direct action as in the case of saturated hydrocarbons.

In probably every aldehyde and ketone there is present at least some of an isomeric compound that is formed by wandering of a hydrogen atom. Thus, acetone undoubtedly consists of a mixture in equilibrium.



Such a rearrangement is called tautomerization, and the two compounds are said to be tautomers of each other. The alcohol formed from a ketone in this way is called an enol, and the name has been extended to take in like substances from aldehydes. From acetaldehyde would be obtained the theoretical vinyl alcohol.



The amount of enol that is present in simple ketones and aldehydes of the aliphatic series probably is extremely small, but in some special cases, like acetoacetic ester (q.v.), the enol form may become very important.

USE IN PHARMACY

Formaldehyde Solution U.S.P. (Formalin, Formol). Formaldehyde Solution is a colorless, aqueous solution containing "not less than 37 per cent of HCHO with variable amounts of methanol to prevent polymerization." It is miscible with water or alcohol and has the pungent odor that is typical of the lower members of the aliphatic aldehyde series.

Owing to the ease with which oxidation and polymerization can take place, the chief impurities to be found in the solution are formic acid and paraformaldehyde. The U.S.P. limits the amount of acid to 0.23 per cent, and methyl alcohol is added to prevent formation of the polymer, although on long standing, especially in the cold, the solution may become cloudy. It should, therefore, be preserved in tightly closed containers at temperatures not below 25° C.

Assay is performed by oxidation to sodium formate with hydrogen peroxide and a vol-

umetric solution of sodium hydroxide. After heating the mixture on a water bath for 5 minutes, the excess of alkali is determined by titration with normal sulfuric acid. One of the tests for identity involves the reduction of an ammoniacal solution of silver nitrate to a precipitate or mirror of metallic silver. Another test depends upon the deep red color produced by warming with a solution of salicylic acid in sulfuric acid.

Formaldehyde was first prepared by Hofmann (1868) by passing a hot mixture of methyl alcohol and air over platinum. It is still obtained commercially in the same way, although a variety of catalysts have been utilized, including copper, silver, oxides of iron and molybdenum and vanadium pentoxide. It also can be produced by the oxidation of methane in natural gas¹ or by the reduction of formic acid. Formaldehyde does not occur naturally in significant amounts, although many plant physiologists believe it is an intermediate in photosynthesis (see chlorophyll). It is often found in the aqueous distillate during the preparation of volatile oils from plants.

Formaldehyde differs from typical aliphatic aldehydes in some important reactions. When evaporated with a solution of ammonia, it forms methenamine by condensation.

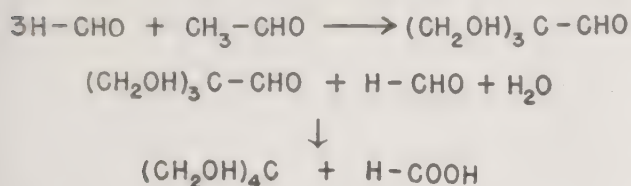


When warmed with alkali, it yields no resin but partly undergoes the Cannizzaro reaction, which is characteristic of any aldehyde that has no alpha hydrogen atom.



However, it will give an aldol condensation if allowed to stand for some time with dilute alkali, finally producing a mixture of sugars known as formose; both pentoses and hexoses have been isolated from this. In addition, formaldehyde will perform an aldol condensation with other aldehydes, and the product usually will give the Cannizzaro re-

action. With acetaldehyde and calcium hydroxide, for example, it furnishes pentaerythritol and a formate.



Finally, it shows a remarkable tendency to polymerize, since plain evaporation of the solution yields a white, friable mass of paraformaldehyde. If a strong solution is distilled with 2 per cent sulfuric acid and the vapors are condensed quickly, a crystalline trimer known as trioxane or trioxymethylene is formed. Either one of these products can be depolymerized by heat, thus giving a convenient source of formaldehyde for synthetic and other processes.

It will also condense with a great variety of other compounds. Any active hydrogen, whether it is attached to carbon, nitrogen or oxygen, will react with the carbonyl group to produce water, either with or without primary addition. In this way, formaldehyde becomes a very useful synthetic agent and frequently is employed for the manufacture of medicinals, dyes, plastics, etc. From the pharmaceutical viewpoint, one of the most important of these reactions is that on amino acids and proteins. Formaldehyde adds to the amino group to mask its basic character, thus making it possible to measure carboxyl value in the so-called formol titration. The nature of this primary effect is not known with certainty, but we may assume it to be addition to yield the grouping $\text{CH}_2\text{OH}-\text{N}=\text{}$. However, the action does not stop there; undoubtedly there is an elimination of water and a primary alteration of the protein molecule (denaturing). The final result on animal or vegetable tissue is a coagulation and hardening, an irreversible process.

Formaldehyde, either as a gas or in solution, has a powerful effect on all kinds of tissue; it is irritating to mucous membranes,

hardens the skin and kills bacteria or inhibits their growth. It is an excellent germicide, probably equal to phenols or mercury, and its volatility renders it more penetrable. A dilution of 1:5,000 inhibits the growth of any organism, and, in many cases, 1:20,000 will retard any multiplication. Large doses by mouth cause the usual symptoms of gastro-enteritis and ultimate collapse. When inhaled, the gas is very irritating, so much so that it may bring about a bronchial catarrh.

The gas has been employed to disinfect rooms, excreta, instruments and clothing, for which purposes it is very efficient. An infected room may be purified by mixing the solution, about 1 pound to every 1,000 to 1,500 cubic feet, with an equal amount of chlorinated lime, one-fourth as much of potassium permanganate, or a corresponding quantity of similar agents, and closing the room for 24 hours. Temperatures above 15°C . are essential, and the presence of moisture is of great assistance. Insects and vermin are not greatly affected.

Usually, applications to the body are not to be recommended, but they are used sometimes. Diluted with water or alcohol, the solution has been applied as hardener of the skin and to prevent excessive sweating, also to disinfect the hands or the site of an operation. A 1 per cent jelly of the official solution or a dusting powder has been employed in eczemas and other skin diseases, and applications in full strength have been made to treat ringworm and to remove warts and moles. It has even been used as a vapor in respiratory infections or as the diluted solution in tonsillitis, ozena or tubercular laryngitis. A 1:1,000 to 1:5,000 solution has been employed in the eye for trachoma, but the process is very painful unless a local anesthetic is administered. It is an excellent preservative for food, but this is usually prohibited by law.

Industrially, formaldehyde has a considerable number of important and varied uses. The mere fact that more than 250,000 tons

of the solution are manufactured in the United States annually is a striking illustration. It is indispensable in the manufacture of certain phenolic resins, urea plastics, mirrors, some kinds of rayon, dyes, esters of cellulose, explosives, photographic plates and papers, embalming fluids and many organic chemicals. It is also used in photographic processes, with dyes to improve fastness, to aid the tanning process, to preserve and coagulate rubber latex and to prevent mildew in vegetable products.

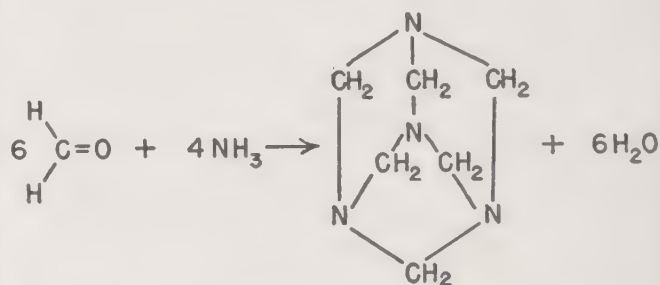
Paraformaldehyde, obtained by evaporating a formaldehyde solution, is also known as paraform, triformol and erroneously, trioxymethylene. It is a white powder that is slowly soluble in cold water and more readily soluble in hot water, but with some decomposition to produce an odor of formaldehyde. Because it can be completely converted to the gas by heating, it is largely used as a convenient form of transportation. It has been employed both externally and internally in medicine, but its therapeutic value is questionable.

Sodium Formaldehydesulfoxylate, ($\text{CH}_2\text{OH}-\text{SO}_2\text{Na}\cdot 2\text{H}_2\text{O}$), also known as rongolite, formopone and hydrolit, is made by reducing the sodium bisulfite addition product of formaldehyde by zinc dust and acetic acid. It consists of white crystals or pieces that are soluble in water but only sparingly so in alcohol. It is almost odorless when freshly prepared but quickly develops a characteristic garliclike odor. It is rapidly decomposed by acids and will reduce even very mild oxidizing agents.

The compound was introduced into medicine by Rosenthal² in 1934 as an antidote for mercury poisoning. He recommended washing out the stomach with a 2 per cent solution and intravenous injection of 5 to 10 grams in 150 cc. of water. Orally, it affords protection to the mucosa and renders insoluble any unabsorbed mercury. Even after injection, the toxicity is low, and the antidotal effects are presumed to be exerted for several hours. More recent experience

has indicated that, while it does have some antidotal effect, the practical clinical value is not high.

Methenamine (**Hexamethylenamine**, **Hexamethylenetetramine**) U.S.P. is also known as urotropin, formin, cystogen, hexamine, aminoform and cystamine. It is actually not an aldehyde at all, but its value depends upon the liberation of formaldehyde, and, therefore, it should be considered at this point. It is manufactured by evaporating a solution of formaldehyde to dryness with strong ammonia water.



The compound consists of colorless crystals or a white crystalline powder without odor. It sublimes at about 260°C . without melting and burns readily with a smokeless flame. It dissolves in 1.5 cc. of water to make an alkaline solution and in 12.5 cc. of alcohol. Warm acids will liberate formaldehyde, which may be recognized by its odor, and the subsequent additions of alkalis will give an odor of ammonia. The assay of the compound depends upon decomposition with volumetric solution of sulfuric acid and titration of the excess with sodium hydroxide.

Methenamine is used internally as an antiseptic, especially in the urinary tract. In itself it has practically no bacteriostatic power and can only be efficacious where it is acidified to produce formaldehyde. Because concentration in the kidney and bladder can never become very high, the success in treating infections of the urinary tract has usually not been great. In order to obtain a maximum effect, the administration of the compound is generally accompanied by sodium biphosphate, ammonium chloride or a similar acidifying agent. The official dose of

methenamine is 0.5 gram, but larger doses are often employed.

OFFICIAL OCCURRENCE

U.S.P.

Methenamine Tablets

N.F.

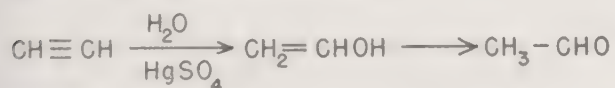
Methenamine Ampuls

Methenamine and Sodium Biphosphate Tablets

Methenamine Tetraiodine (Siomine) N.N.R. is an iodine addition product and is used only for its content of iodine, 78.5 per cent. It is a red powder with a slight odor and taste and is almost insoluble in water. It is administered in capsule form in doses of 0.06 to 0.3 gram.

A large number of salts and other derivatives of methenamine have been introduced into medicine with claims of advantages, but most of them have been abandoned. Among these might be mentioned Mandelamine (mandelate) which is at present sometimes used, Hexalet (sulfosalicylate), Helmitol (anhydromethylenecitrate) and Salihexin (acetylaminosalicylic acid derivative).

Acetaldehyde is becoming of very great importance because of the variety of compounds that can be made from it. It can be manufactured from ethyl alcohol by vapor phase oxidation, from acetylene by hydration and from petroleum hydrocarbons by oxidation with air at about 500° C., products from the last including formaldehyde and methyl alcohol. In the acetylene method, the gas is passed into a solution of mercuric sulfate in dilute sulfuric acid at somewhat above room temperature. The acetaldehyde is distilled off as fast as it is formed and is purified by refractionation.



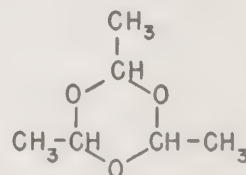
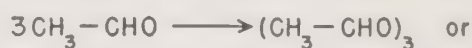
It is not sold as such in very large quantity, but is immediately transformed into other compounds on the spot. The largest use is in the production of acetic acid and its anhydride and in making ethyl acetate.

The polymerization of acetaldehyde in the presence of a small amount of sulfuric acid

gives liquid paraldehyde. If the reaction is conducted below 0° C., the product is the solid tetramer called metaldehyde and marketed as a solid fuel under the title of "Meta." Either of these can be converted to acetaldehyde by heating with dilute acid. They give none of the reactions of aldehydes.

Paraldehyde (Paracetaldehyde) U.S.P. is a colorless liquid with an odor that is not unpleasant and a disagreeable taste. It has a specific gravity of about 0.99, boils at from 120 to 126° C. and congeals at about 11° C. It dissolves in about 8 cc. of water, but is less soluble in hot water, and it is miscible with the usual organic solvents.

To prepare it, cold acetaldehyde is treated with a small amount of concentrated sulfuric acid, and after a few minutes, the catalyst and excess aldehyde are washed away with water or dilute alkali. The product is then dried and distilled.



The chief impurities to be expected are acetaldehyde, the amount of which can be determined by reaction with hydroxylamine, and acetic acid that may be formed by oxidation. It should be preserved in well-filled, tight, light-resistant containers which hold not more than 120 grams, preferably at a temperature not above 30° C.

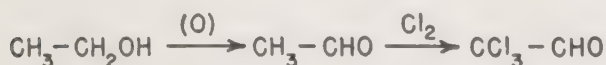
The physiologic action of paraldehyde is similar to that of alcohol, but with greater prominence to the hypnosis and with fewer symptoms of excitement. Therapeutic doses cause sleep that is indistinguishable from a natural one and is accompanied by little change in respiration or circulation. Much greater amounts produce a deep coma and some depressant action upon the respiration, without markedly altering the flow of blood. It is undoubtedly the safest of hypnotics. The chief objections to its use are the dis-

agreeable taste and the fact that an unpleasant odor remains on the breath for several hours.

It is employed in medicine to a limited extent as analgesic and hypnotic. By rectal injection, large doses (1.3 cc. for each 10 pounds of weight) have been given during childbirth, but the method is somewhat dangerous. The most useful fields for its administration are in delirium tremens and in the treatment of mental cases, where drugs must be given over long periods. The official dose of 4 cc. is often greatly increased.

Chloral Hydrate (Chloral)* U.S.P. is one of the oldest synthetic drugs, having been introduced into medicine nearly 80 years ago. In recent times, it has been largely supplanted by barbitals, but it is a reliable hypnotic and is still the standard by which other drugs of the class are judged.

Anhydrous chloral is prepared by the action of chlorine on ethyl alcohol in the presence of a base. The reaction is not simple, but the final result is as if it were merely oxidation and chlorination.



The product is a colorless, oily liquid with a pungent odor and gives most reactions that are typical of aldehydes. If kept for some time, it is transformed to a solid polymer, but in the presence of water is immediately converted to the hydrate. A by-product that often crystallizes from the mixture is chloral alcoholate, a hemiacetal, $\text{CCl}_3\text{--CHOH--O--C}_2\text{H}_5$; it is a crystalline solid that melts at 65°C. and is slowly converted to chloral hydrate by water.

Chloral hydrate occurs as colorless, transparent or white crystals having an aromatic, penetrating and slightly acrid odor and a bitter, caustic taste. It dissolves in water (1:0.25) in alcohol (1:1.3) and in chloroform, ether or oils. The aqueous solution is neutral to litmus paper. It hydrolyzes

* The official synonym for chloral hydrate is not a proper one since chloral is quite a different compound.

readily with strong alkalis to give chloroform and a formate, a reaction that is utilized in the official assay. When it is warmed with aniline and a base, the odor of phenyl isocyanide (phenyl carbylamine) is observed, a typical reaction of chloroform.

Chloral hydrate causes local irritation and some anesthesia and is mildly antiseptic. In the alimentary tract it is irritant and apt to cause nausea, vomiting and purging, although absorption is moderately rapid. Therapeutic doses slow the heart and reduce the blood pressure and respiration to a limited degree, but mainly act on the cerebral centers to produce sleep. The sensory centers are affected very little, so that its efficiency as hypnotic is reduced in the presence of much pain. The very nearly natural sleep lasts several hours, and the patient suffers a minimum of discomfort and after-depression.

It has been used for many years as a reliable and safe hypnotic in insomnia that is not caused by pain; it is very efficient even in obstinate forms such as delirium tremens and mental disorders. It is also effective as a nervous sedative in seasickness, hiccough, the delirium of fevers, and in hysteria. As an anticonvulsant, it is often prescribed in chorea, asthma and whooping cough. It is best administered in a flavored vehicle to disguise the taste and well diluted to prevent gastric disturbance. Seldom is it necessary to use more than the official dose of 0.6 gram, but three times this amount is comparatively safe. Locally, with camphor or menthol, it has been employed for the relief of rheumatism, toothache, neuralgia and itching skin diseases.

Hydro-alcoholic solutions of chloral hydrate, especially with certain salts, often separate into two layers, largely due to the formation of chloral alcoholate. This does not happen when the percentage of alcohol is low enough (about 10 per cent). The toxicity and potency of the alcoholate are less than those of chloral hydrate.

Many derivatives and combinations of

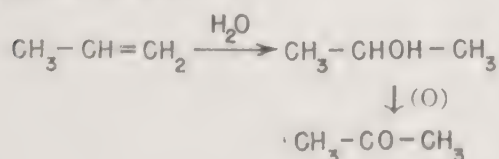
chloral have been introduced in order to eliminate its disadvantages. Very few of these have survived because they are just as objectionable or are unreliable in action. Among these are Dormiol (chloral amylene hydrate), Chloralformamide (q.v.) and Chloralose (a combination of chloral and dextrose). The average dose is 0.6 Gm.

Butylchloral Hydrate N.N.R. $[\text{CH}_3\text{—CHCl—CCl}_2\text{—CH(OH)}_2]$ occurs as pearly-white crystals with a pungent odor and an acrid taste. It is not very soluble in water (1:50) but dissolves readily in alcohol. It is used in the same way as chloral hydrate in doses of 0.3 to 0.6 gram.

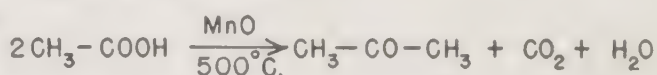
Acetone (Dimethyl Ketone) N.F. was first observed in the distillate from wood in 1661 by Robert Boyle; it was isolated from the heating of acetates by Macaire and Marcet in 1823. A small amount is present in normal blood and urine; this may be increased greatly in diabetes, apparently by decarboxylation of acetoacetic acid. It was formerly manufactured by heating acetates or by the distillation of wood, but practically all of the annual production (about 120,000 tons) today is made from petroleum or from starches by fermentation.

The fermentation method, developed since 1914, first utilized corn starch and *Clostridium acetobutylicum* Weizmann. The chief products are *n*-butyl alcohol, acetone and ethyl alcohol in the proportion of about 6:3:1. Other organisms were also found for this process, as well as a variety of raw materials including potatoes, molasses, bran and other waste from plants. By altering the factors, acetone can be obtained as the chief product.

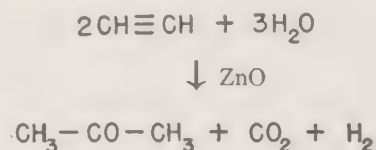
The usual starting material from petroleum is propylene, which can be produced in almost unlimited amount by the cracking process. This is catalytically hydrated to isopropyl alcohol, and this may in turn be oxidized to acetone.



Other methods are available to utilize ethylene from the cracking process, either through ethyl alcohol or acetaldehyde. A similar method of some commercial importance involves the use of acetylene, which is first converted to acetaldehyde (q.v.) and acetic acid. Vapors of the last are passed over manganous oxide or other catalytic agents at 400–500° C.



Furthermore, it is also possible to convert acetylene directly to acetone by hydration, using zinc oxide as catalyst.³

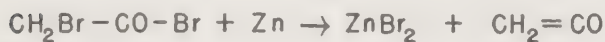


Commercial acetone is usually of a high degree of purity, seldom less than 99 per cent, the remainder being practically all water. It is a transparent, colorless, mobile liquid with a characteristic odor, boiling at about 56° C. but volatile and inflammable at much lower temperatures. It has a specific gravity of about 0.79 and is miscible with water, alcohol or other solvents. Like other methyl ketones, it gives the haloform reaction. With sodium nitroprusside in the presence of alkalies, it gives a red color that is deepened by the addition of excess acetic acid.

Although acetone is not used in medicine, it is of immense value in industry, chiefly as a solvent for fats, waxes, oils, varnishes, lacquers, rubber, etc. In addition, it is employed in the manufacture of a great number of substances, including chloroform, iodoform, explosives, varnish removers, plastics, rayon and medicinals. It is added to tanks of acetylene to aid in compression and to make it safe from explosion, for acetone will dissolve 24 times its volume of the gas.

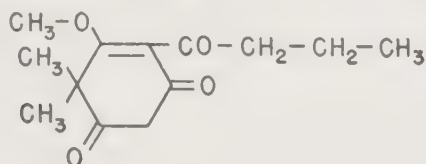
Other aliphatic ketones of note are: amyl methyl, amyl ethyl, hexyl methyl, heptyl methyl and methyl nonyl ketones; methyl-heptenone, $\text{CH}_3\text{—CO—CH}_2\text{—CH=}$

$C(CH_3)_2$, and diacetyl, $CH_3-CO-CO-CH_3$. All of these are found in the products obtained from distilling certain plants with steam. One important compound that should be mentioned is ketene, which can be made from acetone by heating it to $750^\circ C$., by dehydrating acetic acid or by treating bromoacetyl bromide with zinc dust.



This compound is a highly reactive gas that is much used in synthetic processes. Other ketenes, $R-CH=CO$ and $R_2C=CO$, are made in a similar manner from acid derivatives.

Aspidium U.S.P., which is used as an anthelmintic, contains a number of compounds that are derived from filicinic acid, 1,1-dimethylcyclohexan-2,4,6-trione. The most important of these are aspidinol, albaspidin and flavaspidic acid, all of which contain butyryl groups. As verified by synthesis, aspidinol⁴ has the structural formula



Numerous other alicyclic ketones are found in nature or are important in other ways. Those in volatile oils are mostly terpene derivatives and will be described elsewhere. They include jasmone, ionone, irone, camphor, thujone, carvone, pulegone, piperitone, menthone, civetone, muscone and diosphenol. Other important groups are the quinones and certain of the steroids.

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9

Aliphatic Carboxylic Acids and Their Derivatives

SATURATED MONOBASIC ACIDS

ESTERS

DERIVATIVES OF SATURATED MONOBASIC ACIDS

DERIVATIVES OF POLYBASIC ACIDS

UNSATURATED MONOBASIC ACIDS

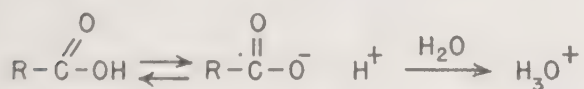
SOAPS

HALOGENATED ACIDS AND SALTS

FATS AND OILS

ESTERS OF INORGANIC ACIDS

Organic acids are characterized by having one or more carboxyl groups (COOH) in the molecule. They are often referred to as monocarboxylic (monobasic) acids, dicarboxylic (dibasic) acids, tricarboxylic (tribasic) acids, etc. The structure of the carboxyl group is such that an organic acid will ionize sufficiently to provide hydrogen (hydronium, H_3O^+) ions.

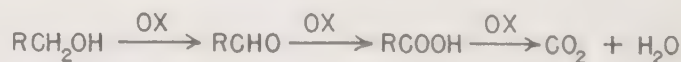


Organic acids are weak acids since they ionize but slightly in polar solvents such as water.

Just as the alcohols may be thought of as hydrocarbons having a hydrogen replaced by a hydroxyl group (OH), so may the acids be considered as hydrocarbons having a carboxyl group replacing a hydrogen atom. The simplest acid would then be the methane derivative, acetic acid, CH_3COOH . Formic

acid, HCOOH , is a hydrocarbon derivative but is unusual in that the carboxyl group is attached to a hydrogen atom and thus becomes the simplest organic acid.

Organic acids are the final oxidation product of primary alcohols and of aldehydes before the breakdown of the carbon chain to carbon dioxide and water.



The carboxylic acids may also be looked upon as being derived from water (HOH) by the replacement of a hydrogen atom with

an acyl group ($\text{R}-\overset{\text{O}}{\parallel}\text{C}-$). The term "fatty acids" applies to the straight chain acids having an even number of carbon atoms from C_4 to C_{18} . They are so called because such acids are found as glyceryl esters in fats and oils. Fatty acids may be saturated or un-

saturated and may or may not contain hydroxyl groups. Fat acids is the name often used to denote the acids of the acetic acid series, which, of course, are all saturated; the series includes acids with even and uneven-numbered carbon atoms.

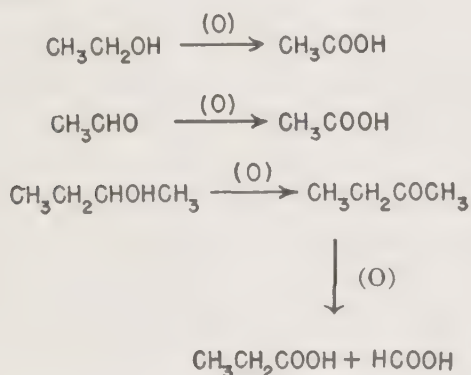
As a general rule, introduction of the carboxyl group into any organic molecule tends to increase solubility in water and to decrease both toxicity and physiologic action.

SATURATED MONOBASIC ACIDS

The monobasic saturated acids and their esters and salts represent an important group of organic compounds used in pharmacy. Aliphatic straight-chain acids up to C_{10} , and those of even-numbered carbon atoms up to C_{18} have been found in nature. Also, the acids of C_{11} and C_{17} have been reported.

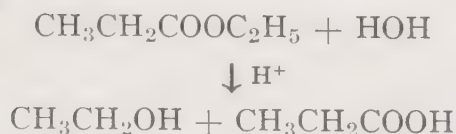
Preparation of these acids may be carried out in many ways, of which the following are typical:

1. OXIDATION OF ALCOHOLS, ALDEHYDES OR KETONES.

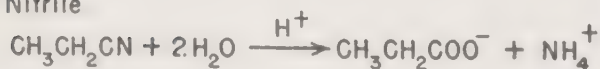


2. HYDROLYSIS OF ACID DERIVATIVES.

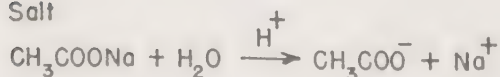
Ester



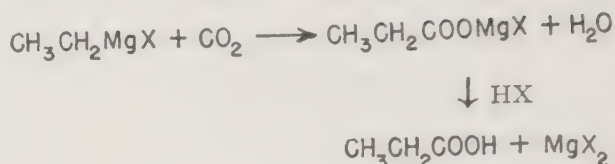
Nitrile



Salt



3. GRIGNARD REACTION.



The melting points of the aliphatic saturated acids increase with an increase in the number of carbon atoms. They are liquids up to C_8 and C_9 , and the higher members are waxy solids. The lower members are soluble in water (formic, acetic and propionic acids), but as molecular weight increases, the solubility in water decreases. All are soluble in organic solvents, including methyl and ethyl alcohols. They dissociate very slightly in aqueous solution. The sodium and potassium salts are soluble and are frequently employed as buffers. The salts formed with other metals such as Ca, Ba, Mg, Sr, etc., are insoluble in water. Those acids of low molecular weight have characteristic odors, but the higher ones of eight carbon atoms or more are odorless.

A carboxyl group present in an organic compound provides the characteristic chemical properties which are associated with organic acids. These compounds exhibit acid properties, and suitable methods may be used to cause the replacement of the hydrogen atom by metals or acyl groups (RCO): the hydroxyl of the carboxyl groups may be substituted by the groups RO, SH, NH_2 , Cl_3 , Cl, H or RCOO; the oxygen and hydroxyl may be substituted by hydrogen (reaction known as decarboxylation). In general, the acids are resistant both to oxidation, which results in carbon dioxide and water, and to reduction, which results in aldehydes and alcohols.

The physiologic activity possessed or conferred by the carboxyl group is limited and generally insignificant. As previously noted, the tendency is for a compound to decrease in activity upon the introduction of a carboxyl group, but at the same time it may assume entirely new and yet useful properties. Note the difference between methane and

acetic acid and between acetic acid and malonic acid. The physiologic activity of the straight-chain even-numbered acids is negligible since they are available from many foods (fats) and are readily oxidized by the body. Lower members are corrosive in a concentrated form but not when diluted. Like the alcohols and hydrocarbons, the branched chain acids are more active physiologically than are their straight chain isomers. The hypnotic property of the drug valerian was thought to be due to valeric acid. Several valeric acid esters and urea derivatives, some brominated, have been introduced as sedatives into medicine. The alpha hydrogen atoms of acetic acid also may be substituted by alkyl groups, such as $(\text{CH}_3)_3$ and $(\text{CH}_3)_2(\text{C}_2\text{H}_5)$, thus producing an active hypnotic compound.

ESTERS

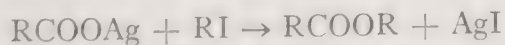
Next to the salts of acids, their esters represent the most important acid derivatives used in pharmacy and medicine. The esters may be considered as organic acids with the hydroxyl of the carboxyl group replaced by an alkoxy group (RO). Numerous examples of ester-type compounds (RCH_2COOR) are to be found among the therapeutic agents; such compounds are atropine, cocaine, fats, waxes, most local anesthetics, etc.

Many procedures are available for the preparation of esters. Some of the most commonly used methods are the following.

1. The action of an alcohol on an acid with the aid of heat and some mineral acid (HCl or H_2SO_4) as a catalyst (Fischer Method).



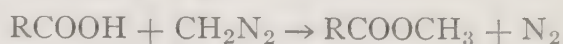
2. The action of an alkylating agent on the sodium or silver salt of an acid.



3. The action of an acid chloride on an alcohol.



4. For the methyl ester, the action of diazomethane on an acid.



The carboxylic acid esters are neutral liquids or solids which are hydrolyzed, slowly by water and rapidly by acids or alkalies, into their components. In the case of alkalies, the salt of the acid is obtained. The simpler esters are liquids and possess a fragrant odor, whereas, the acids have a pungent or nauseating smell, e.g., ethyl butyrate has the odor of pineapple, while butyric acid has the odor of rancid butter.

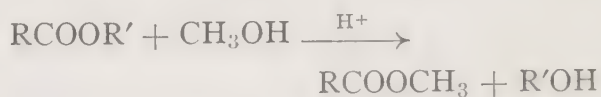
A few of the very simple esters are soluble in water, but those composed of more than four carbon atoms are practically insoluble in water.

Certain chemical reactions are characteristic of esters, and the use of these reactions provides methods of producing compounds that are otherwise hard to obtain. Esters are reduced to alcohols by suitable methods, for example, catalytic reductions and the use of sodium and alcohol.

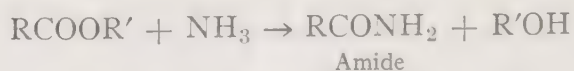


Hydrolysis of esters provides a method of obtaining acids or acid salts.

Ester interchange (alcoholysis) is useful in preparing the methyl or ethyl ester of an acid. By using an excess of methyl or ethyl alcohol, an acid catalyst and heat, one can cause most esters, including glycerides, to be a source of the methyl or ethyl ester of the acid.



Amides generally can be prepared by the action of ammonia on an ester.

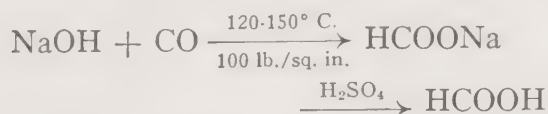


DERIVATIVES OF SATURATED MONOBASIC ACIDS

Formic Acid N.F. The simplest organic acid, formic acid, derives its name from the red ant (*Formica rufa*) from which it was

first isolated. It is also found in the stinging nettle, pine needles, caterpillars and in some plants and fruits.

It may be prepared by several methods, but is usually obtained by treating sodium hydroxide with carbon monoxide; then, to liberate formic acid, sulfuric acid is added to the sodium formate thus formed.



Formic acid of about 85 per cent purity may be prepared, although a 25 per cent solution is usually used commercially.

The acid is a colorless liquid having a characteristic pungent odor and is soluble in water, alcohol, glycerin or ether. It is the strongest aliphatic acid, and because of the

aldehyde group present $\begin{array}{c} \text{O} \\ \parallel \\ \text{—C—} \\ \diagdown \\ \text{H,} \end{array}$ possesses

the properties of both aldehydes and acids. The acid is, as is formaldehyde, a strong antiseptic and reducing agent, producing free silver when warmed with ammoniacal silver nitrate.

Formic acid is corrosive and irritating. Diluted, it is relatively nontoxic when ingested, as it is readily oxidized to carbon dioxide and water. It has some use in industry, but is of doubtful value in therapeutics. In agriculture, it is used as a fungicide for smut, etc.

The average dose is 0.12 to 0.3 cc.

OFFICIAL OCCURRENCE	PER CENT FORMIC ACID
N.F.	
Formic Acid Spirit.....	1.0

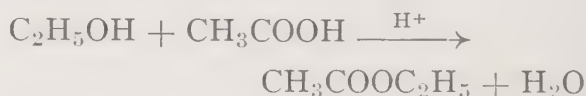
Acetic Acid N.F. (Ethanoic Acid). Acetic acid and its salts and esters are widely distributed in nature. The acid has been known for over a hundred years, first in the form of vinegar. Acetic acid has been obtained from many sources but is now produced from ethanol by oxidation and from acetylene by hydration to acetaldehyde, which is then oxidized.



Acetic acid is a corrosive, colorless liquid with a pungent odor and a sharp, acid taste. It is nontoxic and of little therapeutic value. Acetates such as those of lead, aluminum and zinc, are prepared from it, and it is useful as an industrial solvent.

OFFICIAL OCCURRENCE	PER CENT ACETIC ACID
U.S.P.	
Glacial Acetic Acid	99.4
Acetic Acid	36.0
N.F.	
Diluted Acetic Acid	6.0
Acetic Turpentine Liniment.....	2.8
Aluminum Subacetate Solution...	16.0
Aluminum Acetate Solution.....	1.5
Cantharides Cerate	2.5
Cantharides Tincture	10.0
Iron and Ammonium Acetate Solution	<1.0
Acetic Larkspur Tincture.....	1.8
Lobelia Fluidextract	1.8
Lobelia Tincture	0.18
Squill Vinegar	6.0
Squill Syrup	3.0

Ethyl Acetate (Acetic Ether) N.F., an ester of ethanol and acetic acid, is readily prepared by the Fischer method.



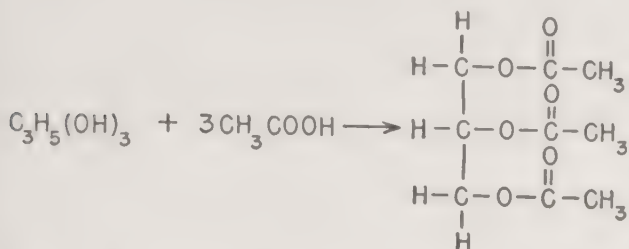
The ester is a clear liquid with a fragrant, fruity odor, and a burning taste. It is miscible with oils or organic solvents and is insoluble in water (1:10).

Ethyl acetate has been suggested for many uses: as a stimulant, an antispasmodic, an antirheumatic, an anesthetic, etc. The present pharmaceutical use is for imparting a pleasant odor and flavor; in industry, it has a wider application as a solvent.

The average dose is 1 to 2 cc.

OFFICIAL OCCURRENCE	PER CENT ETHYL ACETATE
N.F.	
Glycerinated Gentian Elixir ..	0.10
Peptonized Iron and Manganese Solution	0.02
Perfumed Spirit	0.20

Glyceryl Triacetate (Triacetin) U.S.P. is an ester of glycerin and acetic acid prepared by heating a mixture of the two.



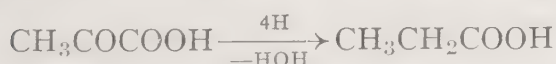
It is a colorless, oily liquid with a fatty odor and bitter taste. It is soluble in water or organic solvents. The primary use is as a solvent for chloroazodin and, recently, triacetin has been used to prepare stable solutions of barbiturates. Such solutions are neither alkaline nor irritating and they may be autoclaved.

OFFICIAL OCCURRENCE
U.S.P.

PER CENT
TRIACETIN

Chloroazodin Solution 99.0

Propionic Acid (Propanoic Acid) has become an important fungicide because it is nontoxic, nonirritant and readily available. Propionic acid is prepared by fermentation, *Propionibacterium* being used on hexoses, pentoses or glycerol.



It is a clear, corrosive liquid with a characteristic odor and is soluble in water. In 1939,¹ Peck, in his studies on perspiration, observed that it was not the pH of perspiration that was responsible for the fungicidal and fungistatic effect but the presence of fatty acids and their salts. Previous to this, Bruce had found that fatty acids of odd-numbered carbon atoms were bacteriostatic while acids of even-numbered carbon atoms were not. Chemical analysis of sweat showed it to contain, among other ingredients, 0.0091 per cent of propionic acid. The fungicidal actions of propionic acid salts such as those of sodium, ammonium, calcium and potassium were found to be the same as that of

the free acid. The free acid may be used to treat fungus infections such as athlete's foot, but is usually employed in the form of its salts because they are more easily handled and are odorless.

Sodium Propionate N.F. (Mycoban). In 1943,² sodium propionate became important as an effective agent in the treatment of fungus infections. The salt occurs as transparent, colorless crystals having a faint odor resembling acetic and butyric acids. They are deliquescent in moist air. It is soluble in water (1:1) or alcohol (1:24). Sodium propionate is most effective at pH 5.5 and is usually used in a 10 per cent ointment, powder or solution. Other fatty acid salts containing an odd number of carbon atoms are just as effective in fungicides but they are more toxic and not so readily available. Undecylenic acid is one that is being used. By 1944, propionate-propionic acid mixtures were found to excel all others, not only as fungicides but also as bactericides. They are only slightly better than the undecylenate-undecylenic acid mixture.

Propionic acid salts of sodium, calcium, potassium and copper are used in preparations for the treatment of fungus infections such as athlete's foot (tinea pedis).

Acid Ammonium Valerate N.F. is a mixture of the salt ammonium valerate and valeric acid. It is a solid complex of one part salt and two parts acid and occurs as colorless, crystalline plates. The crystals are deliquescent, soluble in water or alcohol and sweet-tasting; they have the offensive odor of valeric acid. The attribution of sedative properties to the compound is a result of believing that valeric acid contributed to the activity of valerian. The official salt is inert physiologically.

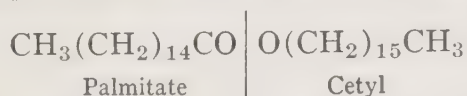
The average dose is 0.13 to 0.6 Gm.

OFFICIAL OCCURRENCE	PER CENT ACID AMMONIUM VALERATE
N.F.	
Ammonium Valerate Elixir	3.5

Sodium Caprylate (C₇H₁₅COONa). Caprylic acid, found in several oils such as coco-

nut and palm-kernel, is the acid from which the sodium salt is prepared. Like propionic acid, caprylic acid is an ingredient of perspiration, where it contributes to the anti-fungicide properties of sweat. It is soluble in water and occurs as a white solid. The salt is effective for the treatment of mucous membrane and cutaneous fungus infections due to *Monibia albicans*.

Spermaceti U.S.P. "is a waxy substance obtained from the head of the sperm whale." The primary constituent is cetyl palmitate,



along with varying amounts of other fatty acid esters and alcohols of high molecular weight. Due to its emollient effects and low melting point (42° to 50° C.), it is used in ointments, creams and cosmetics.

OFFICIAL OCCURRENCE	PER CENT SPERMACETI
U.S.P.	
Rose Water Ointment	12.5

Yellow Wax (Beeswax) U.S.P. (Yellow Beeswax). Yellow Wax "is the purified wax from the honeycomb of the bee, *Apis mellifera* Linné (Fam. *Apidae*).” It is composed primarily of esters, high molecular weight alcohols and acids. The alcohols include those containing 25 to 31 carbon atoms, and the acids range in size from those containing 24 to 34 carbon atoms. Some paraffinic hydrocarbons are also present. It differs from Spermaceti in having acids of higher molecular weight esterified with an alcohol containing 25 to 31 carbon atoms. These esters contribute to the greater hardness and higher melting point of beeswax (62° to 65° C.).

Beeswax is used for its physical properties, primarily in external pharmaceuticals such as ointments, cerates, suppositories, plasters and dressings. Recently, Yellow Wax has been used with peanut oil as a vehicle for penicillin or its salts, in preparations designed for intramuscular injection. The purpose is to decrease the rate of absorption of the penicillin.

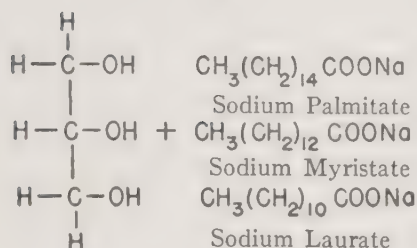
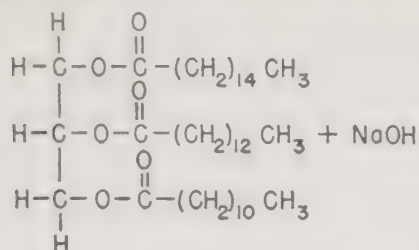
OFFICIAL OCCURRENCE	PER CENT YELLOW WAX
U.S.P.	
Yellow Ointment	5.0
Pine Tar Ointment	15.0
N.F.	
Calamine Ointment	4.0
Cantharides Cerate	17.5
Red Mercuric Oxide Ointment...	5.0
Nutgall Ointment	5.0
Solid Petroxolin	35.0
Compound Resorcinol Ointment .	10.0
Rosin Cerate	15.0
Compound Rosin Cerate.....	22.0
Stramonium Ointment	5.0
Alkaline Sulfur Ointment.....	4.0
Compound Tar Ointment.....	25.0

White Wax (Bleached Beeswax) U.S.P. (White Beeswax). White Wax is yellow wax that has been treated with a bleaching or oxidizing agent. It is practically the same in composition as yellow wax except that the bleaching process produces some free fatty acids and causes the wax to be less unctuous in character.

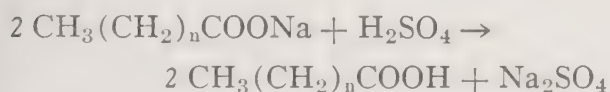
OFFICIAL OCCURRENCE	PER CENT WHITE WAX
U.S.P.	
Strong Mercurial Ointment.....	5.0
White Ointment	5.0
Penicillin Injection in Oil and Wax	...
Hydrophilic Petrolatum	8.0
Rose Water Ointment	12.0
N.F.	
Compound Acetylsalicylic Acid Paste	10.0
Bismuth Paste	5.0
Camphor Ointment	22.0
Cerate	30.0
Lead Subacetate Cerate	20.0
Compound Menthol Ointment ..	5.0
N.F. Sun Cream.....	2.0

Stearic Acid U.S.P. "Stearic Acid is a mixture of solid acids obtained from fats, and consists chiefly of stearic acid [$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$] and palmitic acid [$\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$]." The production of stearic acid is associated with the saponification of fats (beef, tallow, etc.), which procedure is carried out by the use of steam, alkali or by the Twitchell method. Fats are composed of the glycerides of fatty acids. The acids most frequently found are oleic, linoleic, stearic, palmitic and myristic. Saponification of these fats with sodium hy-

dioxide yields the sodium salts of the acids.



The sodium salts are treated with a mineral acid, thus forming the free fatty acids.



Oleic acid and any other unsaturated acids are liquid and readily separated from the solid saturated fatty acids. To prepare pure stearic acid is a difficult task and one that is unnecessary for pharmaceutical use.

Stearic Acid U.S.P. is a solid, white, wax-like, crystalline substance having practically no taste or odor; it is insoluble in water, but soluble in organic solvents.

It is used to prepare stearates and in ointments, suppositories, creams and cosmetic products. The potassium and sodium salts are of special interest, since these are the common soaps. Esters such as glycol stearate are used in ointments, and butyl stearate is satisfactory as an enteric-coating for tablets.

OFFICIAL OCCURRENCE	PER CENT STEARIC ACID
U.S.P.	
Glycerin Suppositories (use permitted)	..
N.F.	
Solid Soap Liniment.....	5.0
Sun Cream	2.0

Glyceryl Monostearate (Monostearin) N.F., $\text{C}_3\text{H}_5(\text{OH})_2\text{OCO}(\text{CH}_2)_{16}\text{CH}_3$, is primarily the monoglyceryl ester of stearic acid, since, due to the method of preparation, some di- and tri- esters are formed. It is a white, waxlike solid having a slightly fatty odor and taste. The ester is insoluble in water, but is soluble in organic solvents. The use of soap or other surface-active agents causes it to be dispersed in aqueous media. Because of the presence of hydrophilic and hydrophobic groups in this molecule, it is valuable as an emulsifying agent and stabilizer in ointments.

Sodium Stearate U.S.P. is "a mixture of varying proportions of sodium stearate ($\text{NaC}_{18}\text{H}_{35}\text{O}_2$) and sodium palmitate ($\text{NaC}_{16}\text{H}_{31}\text{O}_2$). It is prepared by neutralizing Stearic Acid U.S.P. with sodium carbonate.

The salt is used in preparing some ointments, suppositories, creams and cosmetics.

OFFICIAL OCCURRENCE	PER CENT SODIUM STEARATE
U.S.P.	
Glycerin Suppositories	8.0

Zinc Stearate U.S.P. is a compound of zinc with Stearic Acid U.S.P. It is prepared by mixing solutions of equal molar amounts of sodium stearate and zinc acetate. Zinc stearate, being insoluble in water, is washed and removed by filtration. The dry salt is a light, fluffy, fine, white powder which is insoluble in organic solvents.

It is used in ointments and powders as a mild astringent and antiseptic. The salt is a water-repellent powder and was widely used to replace talcum powder until it was found that inhalation may cause pulmonary inflammation.

OFFICIAL OCCURRENCE	PER CENT ZINC STEARATE
N.F.	
Zinc Compounds and Eugenol Cement	1.4

Wool Fat U.S.P. is the purified, anhydrous, fatlike substance from the wool of sheep. Hydrous Wool Fat U.S.P. is wool fat containing 25 to 30 per cent water. This fat-

like material, obtained from the wool of sheep, is a yellow to brown, greaselike, tenacious mass. The composition of wool fat is quite complex, but it contains esters of fatty acids with cholesterol or cholesterol-type compounds as compared with the true fats, which are esters of glycerol. It has certain advantages over the common ointment bases, for example, water absorption, stability and tenacity.

OFFICIAL OCCURRENCE	PER CENT WOOL FAT
U.S.P.	
Boric Acid Ointment.....	5.0
Cupric Citrate Ointment.....	21.0
Strong Mercurial Ointment.	30.0
Ammoniated Mercury Ointment	5.0
White Ointment	5.0
Yellow Ointment	5.0
Hydrophilic Ointment	15.0
Sulfur Ointment	7.0
Zinc Oxide Ointment.....	7.0
N.F.	
Compound Acetylsalicylic Acid Paste	53.0
Benzoic Acid and Salicylic Acid Ointment	5.0
Calamine Ointment	4.0
Ichthammol Ointment	10.0
Lead Subacetate Cerate	20.0
Red Mercuric Oxide Ointment	30.0
Neocalamine Ointment	12.5
Nutgall Ointment	5.0
Compound Resorcinol Oint- ment	28.0
Scarlet Red Ointment.....	40.0
Stramonium Ointment	5.0
Alkaline Sulfur Ointment....	4.0

OFFICIAL OCCURRENCE	PER CENT HYDROUS WOOL FAT
N.F.	
Compound Menthol Ointment	75.0
Mild Mercurous Chloride Ointment	35.0

Lactic Acid N.F. (α -Hydroxy-propionic Acid) is a mixture of lactic acid, $\text{CH}_3\text{CHOHCOOH}$, and lactic anhydride, $\text{CH}_3\text{CHOHCO.OCH}(\text{CH}_3)\text{COOH}$. In 1780, Scheele discovered this product of bacterial fermentation; it is found in such products as sour milk, cheese, buttermilk, wine and sauerkraut.

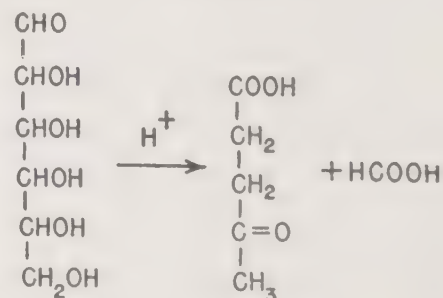
Although lactic acid may be synthesized,

it is commercially produced by the fermentation of molasses, whey or corn sugar, with either *Lactobacillus delbruckii* or *L. bulgaricus*. Because of an asymmetric carbon atom, lactic acid may exist in three forms; it is usually supplied in the *dl* form. The acid is a clear, slightly yellow, odorless, syrupy liquid, miscible with water, alcohol or ether but immiscible with chloroform.

The free acid is seldom used because it is caustic in concentrated form. It is added to infant formulas to aid digestion and to decrease the tendency of regurgitation, and it is employed as a spermatocidal agent in contraceptives. Lactic acid is a natural metabolite of the body and, thus, is used to prepare lactates of minerals which are intended for internal administration, e.g., Calcium Lactate U.S.P., Sodium Lactate Injection U.S.P. and Ferrous Lactate N.N.R. By the use of *Lactobacillus acidophilus*, an acidic intestinal flora which produces lactic acid by fermentation is developed.

OFFICIAL OCCURRENCE	PER CENT LACTIC ACID
N.F.	
Compound Glycerophosphate Elixir	2.0
Compound Pepsin Elixir.....	0.1

Calcium Levulinate N.F. is the hydrated calcium salt of levulinic acid, $(\text{CH}_3\text{COCH}_2\text{-CH}_2\text{COO})_2\text{Ca} \cdot 2\text{H}_2\text{O}$. The acid is produced by heating a hexose (also sucrose, levulose or starch) with dilute hydrochloric acid. The conversion of the carbohydrate to levulinic acid is not clearly understood.



The calcium salt may be prepared using calcium carbonate; calcium levulinate occurs as a powder or white crystals having a bitter taste and faint odor. It is soluble in

water, slightly soluble in alcohol and insoluble in most organic solvents.

The compound is used as a means of administering calcium and is well suited for intravenous injection because of its great solubility in water (1:3). Aqueous solutions are practically nonirritant and may be sterilized by boiling. Usually, a 10 per cent solution is used. The salt also may be given orally just as is calcium gluconate. The average dose is 1.0 Gm.

DERIVATIVES OF POLYBASIC ACIDS

Cerium Oxalate N.F. [$\text{Ce}_2(\text{C}_2\text{O}_4)_3$] is a mixture of oxalates of cerium, praseodymium, neodymium, lanthanum and other associated elements. It is primarily composed of the cerous salt of oxalic acid. Even though oxalic acid is poisonous, the cerous salt is nontoxic and has been used to treat vomiting due to local irritation or to pregnancy. The average dose is 0.2 Gm.

Succinic Acid ($\text{HOOCCH}_2\text{CH}_2\text{COOH}$). Recent studies³ on succinic acid, sodium succinate and magnesium succinate indicate that they are satisfactory in treating chronic constipation. In prolonged use, no nephrotoxic action was observed.

Tartaric Acid U.S.P. (HOOCCHOHCHOHCOOH) is a dihydroxy dicarboxylic acid that was first isolated by Scheele. It is obtained from tartar, a crystalline deposit of crude potassium bitartrate occurring in wine. The acid contains two asymmetric carbon atoms and it exists in *dl*, *l*, *d* and *meso* forms. In the wine industry, a crude form of potassium bitartrate called argol is produced. This is treated with a calcium salt to form insoluble calcium tartrate, which is acidified with sulfuric acid to yield insoluble calcium sulfate and soluble tartaric acid.

The acid occurs as large, colorless crystals or as a fine, white, crystalline powder. It is stable in air, has an acid taste and is odorless. It is soluble in water (1:0.75) or in alcohol (1:3) but it is insoluble in most organic solvents. The properties are typical of those of organic acids and it forms a precipitate with salts of potassium, calcium or iron. The

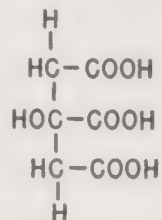
hydrogen of the alcoholic OH is more active than the OH of ethanol and is easily replaced by copper, bismuth, antimony and iron. Thus, there is formed a complex that results in a soluble compound.

Tartaric acid is used in preparing many useful tartrates, and as the free acid, it is employed in effervescent salts and refrigerant drinks. The acid is not decomposed by the body, but it is excreted in the urine and therefore increases the acidity of the system. In comparison with salts of citric acid, tartrates have a greater laxative action. Several salts used as saline cathartics are official, e.g., Potassium Bitartrate, N.F. and Potassium Sodium Tartrate, U.S.P. Bismuth is administered in the form of Bismuth Potassium Tartrate U.S.P. and antimony as Antimony Potassium Tartrate U.S.P. (see Chap. 19).

The average dose is 0.2 to 0.3 Gm.

OFFICIAL OCCURRENCE U.S.P.	PER CENT TARTARIC ACID
Compound Effervescent Powders	
White Paper	100.0
Effervescent Potassium Citrate...	25.2
Effervescent Sodium Phosphate..	25.2

Citric Acid U.S.P. is a tribasic acid that is very widely distributed in nature.



It is the acid present in citrus fruits and berries. Commercially, the acid may be produced from limes or lemons, from the residue from pineapple canning and from the fermentation of beet molasses. Juice from the citrus fruits is treated with chalk, and the precipitated calcium citrate is acidified with sulfuric acid. Calcium sulfate is filtered off and the citric acid is recovered from the filtrate. The fermentation process⁴ accounts for the largest amount of citric acid and may be carried out with any one of over nineteen varieties of fungi (*Citomyces*, *Aspergillus*,

Penicillium, etc.) to give liquor concentrations of from 10 to 15 per cent citric acid.

The acid occurs as a white, crystalline powder or as large, colorless, translucent crystals. It is efflorescent in air, odorless, sour-tasting, and is soluble in water (1:0.5), alcohol (1:18) or ether (1:30), and insoluble in other organic solvents. An aqueous solution of citric acid is unstable because it undergoes slow decomposition. Its chemical reactions are those characteristic of organic acids. Insoluble precipitates are formed with calcium and strontium. The citrate ion is useful to prevent darkening of solutions of iron with tannin; it is an aid in solubilizing other materials such as iron oxide, peptone, caffeine and magnesium.

Therapeutic application of free citric acid is rare, but for a variety of reasons, it has extensive pharmaceutical use. Many salts of citric acid are available and they are used for the benefits of the metal ion, for example, sodium citrate, potassium citrate, cupric citrate, ferric ammonium citrate, green ferric ammonium citrate, soluble manganese citrate and lithium citrate. In some cases the citrate portion contributes to the therapeutic value as it is oxidized to carbonate in vivo.

The average dose is 0.2 to 0.3 Gm.

OFFICIAL OCCURRENCE	PER CENT CITRIC ACID
U.S.P.	
Magnesia Magma	0.1
Citrated Caffeine	50.0
Magnesium Citrate Solution.....	9.4
Orange Syrup	0.5
Effervescent Potassium Citrate....	16.2
Anticoagulant Acid Citrate Dextrose Solution	0.8
N.F.	
Ferrous Sulfate Syrup.....	0.21
Compound Glycerophosphates Elixir	0.06
Pepsin Elixir	1.2
Potassium Citrate Solution.....	0.6
Sodium Citrate Solution.....	2.0
Sodium Phosphate Solution.....	13.0

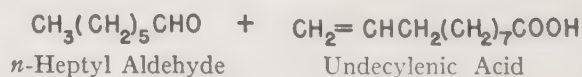
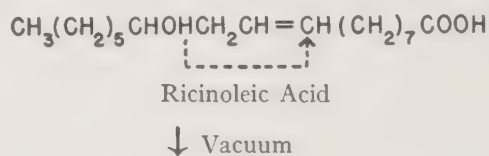
UNSATURATED MONOBASIC ACIDS

A series of unsaturated monobasic acids is possible, of which acrylic acid, $\text{CH}_2=\text{CH}-\text{COOH}$, is the simplest member. Other than crotonic acid, $\text{CH}_3\text{CH}=\text{CHCOOH}$, and

tiglic acid, $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$, rarely is one with less than ten carbon atoms found in nature. The position of the ethylenic linkage also gives to the unsaturated acids the reactivity of the double bond, whereby they enter into all the addition, oxidation and reduction reactions that are characteristic of olefinic hydrocarbons. The carboxyl group, in general, possesses the same characteristics as it does in other acids.

Solubility in water is similar to that found in the saturated series, but the unsaturated acids and their esters are usually liquids.

Undecylenic Acid [$\text{CH}_3\text{CH}=\text{CH}-(\text{CH}_2)_7\text{COOH}$ or $\text{CH}_2=\text{CH}(\text{CH}_2)_8\text{COOH}$]. Undecylenic acid is unsaturated, but the commercial product is not pure, and it contains some oleic and stearic acids. It may be obtained by the destructive distillation of castor oil. The ricinoleic acid, present in castor oil as the glyceride, is the source of undecylenic acid.



The acid melts at 24° C.; it is a soft, opaque mass or liquid at room temperature.

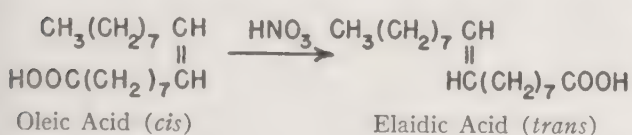
In recent studies,⁵ the higher fatty acids (heptylic, caprylic, pelargonic, capric and undecylenic) have been found to be effective antifungal agents. An undecylenic acid and sodium undecylenate mixture has been found effective in the treatment of fungus infections⁶ such as athlete's foot. At present, there are available preparations that utilize zinc undecylenate or potassium undecylenate.⁷

Oleic Acid U.S.P. [$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$] is an unsaturated acid present as the glyceride in most animal fats and vegetable oils. A process for preparing the pure acid is based on the fact that the lead salt is soluble in ether. A fat or an oil is

saponified with sodium hydroxide, and the sodium salts of the mixed fatty acids are treated with sulfuric acid to yield the free fatty acids. Lead acetate is added to the free acids, thus forming the water-insoluble lead salts. These are then treated with ether, which dissolves the lead salt of oleic acid and also that of any other unsaturated acid present. Ether is removed, and the residue is acidified to yield the free oleic acid. A purification procedure consists of preparing the barium oleate, which can then be recrystallized from alcohol and treated with sulfuric acid to liberate the free oleic acid.

The acid is a light yellow or brown-colored liquid that becomes darker on exposure to air and on standing. It is this unsaturated acid, in the form of olein, which contributes to the low melting point of lard and the fluidity of vegetable oils. The free acid is insoluble in water, but it is soluble in organic solvents. It has a lardlike odor and taste.

Oleic acid exists in the *cis* form and is converted into elaidic acid (the *trans* form) on treatment with nitrous acid, nitrogen tetroxide or nitric acid. This reaction takes place in preparing citrine ointment, as the melting point of elaidic acid is about 44° C. By reduction, oleic acid is converted



into stearic acid, and by oxidation, pellarmonic and aceloic acids result.

It is used in pharmacy in the preparation of oleates and in ointments exclusively. Internally, it causes hemolysis of the red blood corpuscles, an effect which is characteristic of all unsaturated fatty acids.

OFFICIAL OCCURRENCE	PER CENT OLEIC ACID
U.S.P.	
Benzyl Benzoate Lotion	2.0
Saponated Benzyl Benzoate	8.0
Mercury Oleate	75.0
(Mercury Mass N.F.)	
(Strong Mercurial Ointment N.F.)	
Medicinal Soft Soap	2.0

N.F.

Ammonia Liniment	1.0
Stainless Iodized Ointment	20.0
Solid Petroxolin	32.0
Zinc Oxide Soft Paste	2.5
Lead Oleate Plaster (uses olive oil) ...	
Lead Oleate Ointment	...

Linoleic Acid $[\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}]$ and **Linolenic Acid** $[\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}]$. Linoleic and linolenic acids are present in animal tissues. A lack of these acids in the diet leads to eczemas, dry scaly skin and other dermatologic conditions. An external preparation, Linolestrol, containing linoleic and linolenic acids along with lecithin and cholesterol, is available for treatment of these skin conditions. For internal use, there is linocid, a mixture of linoleic and linolenic acids.

Sodium Morrhuate Injection U.S.P. "is a sterile solution of the sodium salts of the fatty acids of cod liver oil." The salt was first introduced in 1918 as a treatment for tuberculosis and, in 1930, it was reported useful as a sclerosing agent. Sodium morrhuate is not a specific substance, although morrhucic acid, $\text{C}_9\text{H}_{13}\text{NO}_3$, has been known for years. Many definitions are given for sodium morrhuate, but generally it can be assumed that it is a mixture of the sodium salts of the saturated and unsaturated fatty acids from cod liver oil.

The preparation of the free fatty acids of cod liver oil is carried out by saponification with alkali and then acidulation of the resulting soap. The free acids are dried over anhydrous sodium sulfate before being dissolved in an equivalent amount of normal sodium hydroxide solution. Sodium morrhuate is obtained by careful evaporation of this solution. The result is a pale, yellowish, granular powder possessing a slight, fishy odor.

Commercial preparations are usually 5 per cent solutions which vary in properties and in color from light yellow to medium yellow to light brown. They are all liquids at room temperature and have congealing points that range from -11° to 7° C. Benzyl alcohol is

present to the extent of 2 per cent as an anesthetic in the injectable solution.

Aqueous solutions of sodium morrhuate are used primarily as sclerosing agents for the obliteration of varicose veins.

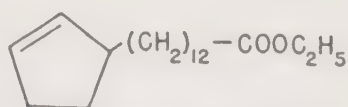
The average dose is 0.5 to 2.0 cc.

Sylansol is a 5 per cent solution of the sodium salt of the fatty acids of a vegetable oil extracted from a seed of the psyllium group. It is used as a sclerosing agent and is claimed to be nontoxic and stable. In comparison with other sclerosing substances, it is less irritating and exhibits less hemolytic action. The thrombosis produced is similar to that of morrhuate solutions.

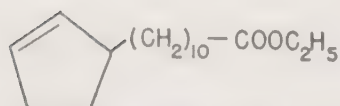
Sodium Ricinoleate Solution N.N.R. (Soricin). Sodium ricinoleate solution $[\text{CH}_3(\text{CH}_2)_5\text{CHOHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COONa}]$ is a sterile, aqueous solution of sodium ricinoleate. The fatty acid, ricinoleic acid, is found in castor oil in the form of the glyceride. It is an example of a hydroxy unsaturated fatty acid. The sodium salt, like most other fatty acids, is irritant to the tissues and is employed, by injection, as a sclerosing agent for the obliteration of varicose veins.

Internally, the sodium salt is used in the treatment of colitis and other intestinal disorders. It may be combined with digestive enzymes and bile salts.

Ethyl Chaulmoograte N.F. "consists of the ethyl esters of the mixed acids of chaulmoogra oil." The oil contains primarily the glycerides of chaulmoogric and hydnocarpic acids. These acids are obtained by saponification followed by acidification and are then esterified with ethyl alcohol.



Ethyl Chaulmoograte



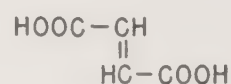
Ethyl Hydnocarpate

The esters form a clear, pale yellow liquid, having a slight fruity odor. It is insoluble in water, but soluble in organic solvents.

Ethyl chaulmoograte is used orally or by injection in the treatment of leprosy or Hansen's disease. It has a less objectionable taste and is less irritating when injected than is Chaulmoogra oil.

The average dose is 0.5 to 5.0 cc.

Fumaric Acid⁸ is the simplest unsaturated dicarboxylic acid; it is a geometric isomer of maleic acid, which is the *cis* configuration.

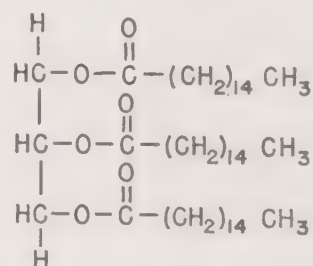


It is obtained as a by-product in a microbiologic chemical synthesis. Fumaric acid and its sodium salt are important as possible substitutes for tartaric acid and its salts. It is less toxic than tartaric acid, and sodium fumarate is of a low order of toxicity.

The sodium salt gives promise of proving a useful agent in treatment of constipation.

SOAPS

A soap is a salt of a fatty acid. Most commonly, a soap is considered as a combination of an alkali (NaOH or KOH) with the fatty acids derived from animal or vegetable oils. A soap of sodium, potassium or ammonium is soluble in water, but most soaps of other metals such as calcium, magnesium, iron, barium, strontium, etc., are insoluble in water.



Palmitin

↓ NaOH

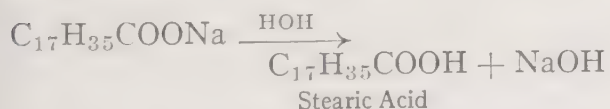


Sodium Palmitate
(Soap)

The preparation of a soap requires the saponification of a fat or oil, primarily containing glycerides, to form a salt. The glycerides most commonly found in lipids are olein, linolein, stearin and palmitin.

Since there is always a mixture of glycerides in fixed oils, the resulting "soap" is always a mixture of the fatty acid salts. The type, kind, grade, etc., of the fat used determines the quality of the soap product. Castile soap, for example, is primarily sodium oleate and it was originally prepared from olive oil. Soaps of sodium are termed "hard" soaps and those of potassium are known as "soft" soaps. Potassium soaps are usually dispensed as liquids or semisolids because it is more difficult to separate this soap from the alkali than it is to separate the more common sodium soaps. The reasons for this are: first the potassium soaps are more soluble than are the sodium soaps and second, it would require a large quantity of potassium chloride, a more expensive salt than sodium chloride, to salt out the potassium soap. When, however, a potassium soap is prepared in the conventional manner, it is found to be just as "hard" as a sodium soap. A laundry soap usually contains gritty material, cosmetic or facial soaps have a perfume incorporated and medicinal soaps have a therapeutic agent such as an antiseptic or fungicide present.

All soaps in aqueous solution undergo hydrolysis and yield free alkali and free fatty acid.



The pH of the usual hand soap is 10 to 11. Other, more crude, soaps are more strongly alkaline because the lack of purification causes some original saponifying alkali to be retained. The detergent effect of soap is, in part, due to the presence of free alkali, which is also responsible for its antiseptic value. A keratolytic or disintegrating action on the skin is likewise a characteristic of soap and is one of the reasons why the alkali content is held at a minimum.

Hard Soap U.S.P. is soap prepared from fats or oils, with sodium hydroxide, and it consists of the sodium salts of the fatty acids. It occurs as white flakes or cakes having a faint odor, freedom from rancidity and slow solubility in water or alcohol. Its uses are most varied, but in pharmacy hard soap is employed primarily as a lubricant and less often as a detergent. Application of it is made in suppositories, tooth pastes, tooth powders, liniments, pills and laxatives.

The average dose is 0.3 to 2.0 Gm.

OFFICIAL OCCURRENCE	PER CENT SOAP
U.S.P.	
Camphor and Soap Liniment.	6.0
Chloroform Liniment	1.8
N.F.	
Solid Soap Liniment	6.0
Aconite and Chloroform Liniment	4.5

Medicinal Soft Soap (Sapo Mollis, Soft Soap, Green Soap) U.S.P. "is a potassium soap made by the saponification of vegetable oils, excluding coconut oil and palm-kernel oil, without the removal of glycerin." It is a soft, unctuous, yellow-to-green-colored mass. The color is due in part to the vegetable oil used and to the age of the soap. These factors also affect the odor.

Sapo Mollis is more strongly alkaline than is Hard Soap U.S.P and thus it has greater detergent properties and irritant action. It is used to cleanse the skin of keratin elements and to stimulate the tissue in some skin diseases. Very rarely is it used internally.

A potassium soap is formed in the preparation of Saponated Cresol Solution.

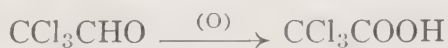
OFFICIAL OCCURRENCE	PER CENT MEDICINAL SOFT SOAP
U.S.P.	
Soft Soap Liniment	65.0
N.F.	
Compound Soft Soap Liniment	15.0

HALOGENATED ACIDS AND SALTS

Dichloroacetic Acid (Bichloroacetic Acid), Cl_2CHCOOH , is a colorless liquid with a characteristic odor. It is a stronger acid than acetic acid, but it is somewhat

less acidic than trichloroacetic acid. The acid is available for use as a keratolytic in the removal of corns, warts and calluses.

Trichloroacetic Acid U.S.P. is one of the three chlorinated acetic acids. It has been known since 1838 and is prepared by oxidizing chloral hydrate with either nitric acid or permanganate.



The acid occurs as colorless, deliquescent crystals that have a characteristic odor. Usually, the introduction of a halogen atom into an acid increases the acidic properties; this is true of acetic acid, the acid properties increase with increase in the number of chlorine atoms. Trichloroacetic acid is a stronger acid (as strong as hydrochloric acid) than acetic acid and is very corrosive to the skin. It is soluble in water (1:0.1) or most organic solvents.

It is astringent, antiseptic and caustic, but the caustic properties are most useful in treating forms of keratosis, such as moles and warts. Solutions of trichloroacetic acid are very efficient protein precipitants.

Sodium Fluoroacetate (1080). In 1944 this compound was found to be an effective chemical for use as a rodenticide. It is a highly poisonous substance, not only for rats, mice, gophers, etc., but for practically all animals and fowls. The LD₅₀ for rats varies from 0.1 mg. to 4.0 mg. per kilogram. Usually, death results from cardiac difficulty, central nervous system depression or a combination of the two. The poison has no effective antidote. Methyl fluoroacetate is also a very toxic material having an LD₅₀ of 0.5 mg./Kg. for horses.

Calcium Iodobehenate U.S.P. (Sajodin, Calioben). Calcium iodobehenate $[(\text{C}_{21}\text{H}_{42}\text{ICOO})_2\text{Ca}]$ is a nearly pure, organic iodine compound. The U.S.P. requires the dried salt to contain not less than 23.5 per cent of iodine, but according to the formula, the pure salt would contain 26.1 per cent iodine. Erucic acid is an unsaturated acid obtained from rape oil. It has the same carbon chain as the saturated acid,

behenic acid. Hydriodic acid (HI) readily adds to the double bond of erucic acid

$[\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{11}\text{COOH}]$, forming a saturated acid, behenic acid, which here has only one hydrogen replaced by an atom of iodine. The calcium salt is prepared because the sodium or potassium salt would be a typical soap, an irritating compound. It is a white or yellowish powder that is odorless or has a slight odor resembling fat. It "is insoluble in water, very slightly soluble in alcohol and in ether, and freely soluble in warm chloroform."

Calcium iodobehenate is an example of the compounds and the preparations (proteins and fats) containing iodine in organic combination. On ingestion, all iodine products release the iodine as the iodide ion, which is distributed evenly in the extracellular fluid. The advantages of organic iodine over the inorganic iodides are slower absorption and less irritation on the digestive tract. Iodides are useful as expectorants, in treating asthma or sinusitis and in tertiary syphilis.

The average dose is 0.5 Gm.

Stearodine (Calcium Iodostearate). Stearodine $[\text{CH}_3(\text{CH}_2)_7\text{CHICH}_2(\text{CH}_3)_7(\text{COO})_2\text{Ca}]$ is the calcium salt of the saturated iodized fatty acid, stearic acid. It is prepared by treating oleic acid with hydrogen iodide. The calcium salt contains about 27 per cent iodine and has the same use as calcium iodobehenate.

Oridine N.N.R. is the calcium salt of the iodized unsaturated fatty acids obtained from cottonseed oil. Iodine in organic combination is present to the extent of 23 to 25 per cent. It is a light-brown powder, insoluble in water and in most organic solvents except chloroform and carbon tetrachloride.

Oridine is used as are the other organic iodine products, as a substitute for inorganic iodides.

The average dose is 10.0 to 30.0 mg.

Iodostar is an iodine derivative of the unsaturated acid, tariric acid $[\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{C}(\text{CH}_2)_7\text{COOH}]$. Two atoms of iodine are added to one mole

of tariric acid to form di-iodotariric acid, $\text{CH}_3(\text{CH}_2)_7\text{CI}=\text{CI}(\text{CH}_2)_7\text{COOH}$. It contains about 47.5 per cent of iodine and occurs as white, crystalline scales. Iodostarine is insoluble in water and slightly soluble in alcohol.

This compound is used, in the form of tablets, for the benefits of the iodides.

Iodobrassid (Lipodine, Lipoiodine) N.N.R. is the ethyl ester of iodobrassic acid,



Brassic acid,

$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{11}\text{COOH}$, does not occur in nature, but is prepared from erucic acid by treatment with nitrous acid. Erucic acid and brassic acid are geometric isomers, just as are oleic acid and elaidic acid. To prepare Iodobrassid, the ethyl ester of brassic acid is treated with two atoms of iodine. It contains 41 per cent iodine and occurs as white crystals which are insoluble in water and slightly soluble in alcohol, soluble in oils or most other organic solvents.

Iodobrassid is employed as a contrast medium for roentgenologic work and as a substitute for inorganic iodides.

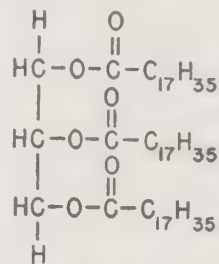
The average dose is 0.3 Gm.

FATS AND OILS

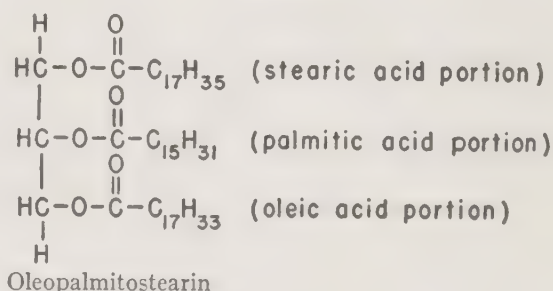
Fats and oils are known as lipid substances, a general name applied to animal and plant products that are composed of esters of glycerin and fatty acids. Fats and oils are differentiated on the basis of melting points: fats are solid at 20°C . and are predominantly mixtures of esters of saturated fatty acids of higher molecular weights (C_{10} or more); oils are liquid at 20°C . and mainly are mixtures of esters of unsaturated fatty acids. A contributing factor may also be esters of low molecular weight fatty acids. The fluidity, or liquid state, of most vegetable oils is generally due to the presence of oleic acid ester with glycerol (olein). In animal fats, the rigidity and high melting point are due to the presence of palmitin and stearin. The composition of fats is di-

rectly responsible for their melting points, i.e., lard $36^\circ\text{--}42^\circ\text{C}$.; beef fat 46°C . and mutton suet $45^\circ\text{--}50^\circ\text{C}$.

Glycerin has three hydroxy groups, each of which may be esterified with the same fatty acid, thus forming a symmetrical glyceride (tristearin); they also may be esterified with two or more different fatty acids, thus forming an unsymmetrical glyceride (oleopalmitostearin).



Tristearin



Oleopalmitostearin

In 1823, the constitution of fats was first explained, and since that time, about fifty fatty acids have been found in nature. All but one are straight-chain acids containing an even number of carbon atoms. The odd-numbered acid is isovaleric acid, which has been isolated from oils of the dolphin and the porpoise.

In Table 11 are listed the important saturated fatty acids containing 4 to 26 carbon atoms.

In Table 12 are given the important unsaturated fatty acids. Those found in fats and oils have an even number of carbon atoms, ranging in carbon content from 10 to 24 atoms.

The physical properties of fats and oils, as a class, are quite varied, yet quite similar and characteristic. They range from liquids to solids of low melting point; they are insoluble in water, nearly insoluble in alco-

TABLE 11. IMPORTANT SATURATED FATTY ACIDS CONTAINING 4 TO 26 CARBON ATOMS

ACID	NUMBER OF CARBON ATOMS	FORMULA	OCCURRENCE AS THE GLYCERIDE
Butyric	4	$\text{CH}_3(\text{CH}_2)_2\text{COOH}$	Butter
Caproic	6	$\text{CH}_3(\text{CH}_2)_4\text{COOH}$	Butter
Caprylic	8	$\text{CH}_3(\text{CH}_2)_6\text{COOH}$	Butter, coconut oil
Capric	10	$\text{CH}_3(\text{CH}_2)_8\text{COOH}$	Butter, coconut oil, palm-nut oil
Lauric	12	$\text{CH}_3(\text{CH}_2)_{10}\text{COOH}$	Coconut oil, spermaceti, palm-kernel oil
Myristic	14	$\text{CH}_3(\text{CH}_2)_{12}\text{COOH}$	Nutmeg fat, coconut oil
Palmitic	16	$\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$	Almost all fats
Stearic	18	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$	Almost all animal fats, cocoa-butter
Arachidic	20	$\text{CH}_3(\text{CH}_2)_{18}\text{COOH}$	Rape-oil, cocoa-butter, peanut oil
Behenic	22	$\text{CH}_3(\text{CH}_2)_{20}\text{COOH}$	Rape-oil, earth-nut oil, ben oil
Lignoceric	24	$\text{CH}_3(\text{CH}_2)_{22}\text{COOH}$	Peanut oil
Cerotic	26	$\text{CH}_3(\text{CH}_2)_{24}\text{COOH}$	Waxes, wool fat

TABLE 12. IMPORTANT UNSATURATED FATTY ACIDS

ACID	NUMBER OF CARBON ATOMS	FORMULA	OCCURRENCE AS THE GLYCERIDE
ONE DOUBLE BOND			
Decylenic	10	$\text{CH}_2=\text{CH}(\text{CH}_2)_7\text{COOH}$	
Undecylenic .	11	$\text{CH}_3\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	
Dodecylenic .	12	$\text{CH}_3\text{CH}_2=\text{CH}(\text{CH}_2)_7\text{COOH}$	
Palmitoleic .	16	$\text{CH}_3(\text{CH}_2)_5\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	
Oleic	18	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	Animal and vegetable oils
Erucic	22	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{11}\text{COOH}$	Rapeseed oil
TWO DOUBLE BONDS			
Linoleic	18	$\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	Linseed oil Cottonseed oil
THREE DOUBLE BONDS			
Linolenic	18	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	Linseed oil
FOUR DOUBLE BONDS			
Arachidonic .	20	$\text{CH}_3(\text{CH}_2)_4(\text{CH}=\text{CHCH}_2)_4(\text{CH}_2)_2\text{COOH}$	Lecithin and cephalin
Clupanodonic	18	$\text{CH}_3(\text{CH}_2)_2(\text{CH}=\text{CHCH}_2)_4(\text{CH}_2)_2\text{COOH}$	Fish oils
ONE TRIPLE BOND			
Tariric	18	$\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{C}(\text{CH}_2)_7\text{COOH}$	Picramnia seed fats
MONOHYDROXY AND DOUBLE BOND			
Ricinoleic ...	18	$\text{CH}_3(\text{CH}_2)_5\text{CH}(\text{OH})\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	Castor oil
CYCLIC AND ONE DOUBLE BOND			
Hydnocarpic .	16	$\text{C}_{15}\text{H}_{27}\text{COOH}$	Chaulmoogra oil
Chaulmoogric.	18	$\text{C}_{17}\text{H}_{31}\text{COOH}$	Chaulmoogra oil

hol and soluble in most other organic solvents. Castor oil is an exception in that it is soluble in alcohol. All will float on water, as they have a specific gravity of less than one. Because they are nonvolatile, they will leave a greasy stain on cloth or paper. The physical consistency and solvent prop-

erties of fats and oils make them desirable vehicles for therapeutic agents.

Fats and oils are chemically classified as esters of the polyhydric alcohol, glycerin, and fatty acids. These esters are known as glycerides. The chemical properties are those of esters, but the fatty acid portion

is responsible for most of their chemical reactions and tests. Glycerides are saponified readily by alkali to form soaps (q.v.) and glycerin. As previously mentioned, the saturated fatty acids form solid glycerides such as palmitin and stearin, whereas the unsaturated fatty acids form liquid glycerides such as olein. Due to the presence of the unsaturated fatty acid glyceride, the vegetable oils contain double bonds and may be "hydrogenated," thereby producing a solid fat. This method is used to produce the many hydrogenated cooking fats that are used as substitutes for lard. Iodine may add to the unsaturated linkage of fatty acid glycerides to produce the iodized oils. Double bonds are responsible for the "drying" properties of oils so that they form a hard film when exposed to air. Vegetable oils are often classified according to their drying ability, with the best drying oils containing a large percentage of the glycerides of linoleic and linolenic acids.

1. Nondrying oils containing a large quantity of oleic acid: palm oil, peanut oil, coconut oil, date oil, olive oil, rice oil.

2. Semidrying oils containing oleic and linoleic acids: corn oil, brazil nut oil, cottonseed oil, soybean oil, sesame oil, rape seed oil.

3. Drying oils containing linoleic and linolenic acids: linseed oil, hempseed oil, tung oil, walnut oil, poppyseed oil, sunflower oil.

Rancidity of fats may be due to oxidative or hydrolytic processes. Oxidative rancidity is the most important and results from the oxidation of the unsaturated residue at the double bond or the methylene groups adjacent to the double bond. This produces, in a fat or oil, short-chained acids, aldehydes and ketones which alter the odor and taste. Many conditions, such as light, heat, moisture and the presence of metals, affect this oxidative process. The double bond or methylene group is, perhaps, first oxidized to a peroxide, which, upon decomposition, oxidizes the fatty acid molecule to yield smaller fragments. Ketones are known to

result from the action of mold on compounds with double bonds. Antioxidants are substances such as siam benzoin, gum guaiac, vitamin E, ethyl gallate and nordihydroguaiaretic acid that tend to stabilize a fat and tend to reduce the tendency to undergo oxidative rancidity.

Hydrolytic rancidity is the breakdown of a glyceride into the acids and glycerin. This chemical change is a serious problem in those fats, like butter, which contain glycerides of fatty acids of low molecular weight and which have a bad odor themselves. Examples of such acids are butyric, caproic, caprylic and capric. Antioxidants are of no value in hydrolytic rancidity. In fats such as lard, suet or tallow, the acids produced are of high molecular weight, odorless and tasteless.

Lard U.S.P. "is the purified internal fat of the abdomen of the hog." It is a white, soft, unctuous mass containing more olein than beef fat or mutton suet. It is used for its emollient properties and in the preparation of ointments and cerates.

OFFICIAL OCCURRENCE	PER CENT LARD
U.S.P.	
Benzoinated Lard	99.0
N.F.	
Camphor Ointment	56.0
Lead Oleate Plaster	33.0
Mercuric Nitrate Ointment....	76.0
Rosin Cerate	50.0
Compound Tar Ointment.....	32.0

Benzoinated Lard U.S.P. is lard containing 1 per cent siam benzoin as an antioxidant and preservative.

OFFICIAL OCCURRENCE	PER CENT BENZOINATED LARD
N.F.	
Cantharides Cerate	20.0
Cerate	70.0
Zinc Oxide Hard Paste.....	70.0

Theobroma Oil (Cocoa Butter) U.S.P. "is the fat obtained from the roasted seed of *Theobroma Cacao* Linné (Fam. *Sterculiaceae*). It contains, primarily, stearin, palmitin, olein and laurin. This mixture of glycerides produces a substance that melts between 30° and 35° C., thus making it very useful as a suppository base.

Prepared Suet N.F. "is the internal fat of the abdomen of the sheep." It is a white, solid fat having a melting point of 45° to 50° C. A high percentage of stearin makes it harder than most other animal fats.

OFFICIAL OCCURRENCE	PER CENT SUET
N.F.	
Compound Rosin Cerate.....	35.0

Olive Oil (Sweet Oil) U.S.P. "is the fixed oil obtained from the ripe fruit of *Olea europaea* Linné (Fam. *Oleaceae*).¹" It contains about 70 per cent olein, and the remainder is mostly palmitin. It has mild laxative properties, but its important uses are as an emollient, a food and in soap manufacture.

The average dose is 30 cc.

OFFICIAL OCCURRENCE	PER CENT OLIVE OIL
N.F.	
Calamine Liniment	50.0
Lead Oleate Plaster.....	33.0
Neocalamine Liniment	50.0
Phenolated Oil	95.0
Scarlet Red Ointment.....	5.0

Castor Oil U.S.P. "is the fixed oil obtained from the seed of *Ricinus communis* Linné (Fam. *Euphorbiaceae*).¹" Due to the presence of the ricinoleic acid residue, the oil is used as a laxative. It is the only fixed oil that is soluble in alcohol, so it is added to collodion to increase the flexibility.

The average dose is 15 cc.

OFFICIAL OCCURRENCE	PER CENT CASTOR OIL
U.S.P.	
Flexible Collodion	3.0
N.F.	
Aromatic Castor Oil	96.5
Salicylic Collodion	2.7

Riodine N.N.R. is a liquid preparation of the iodized, unsaturated fatty acids occurring in castor oil. Castor oil contains about 80 per cent ricinoleic acid in the form of a glyceride; it also contains small amounts of oleic and linolenic acids. The oil is treated with hydrogen iodide until 66 per cent of the unsaturated glycerides are iodized; the result is a product containing about 17 per cent iodine. It is light amber

in color, insoluble in water, but soluble in organic solvents.

Riodine is available in pearls and is used for the effect of the iodide ion.

The average dose is 0.4 to 1.2 Gm.

Cod Liver Oil U.S.P. "is the partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of the family *Gadidae*." Non-Destearinated Cod Liver Oil U.S.P. is the complete, untreated oil. Due to the presence of stearin, it will congeal on cooling and will form a deposit of stearin. Both grades of cod liver oil are of importance because of the vitamins A and D and both are used internally as an aid to nutrition. There is some indication that it is of value in ointment form for the treatment of wounds and burns. The vitamins present appear to be responsible for the ability of the oil to promote healing. Recently, the sodium salt of the fatty acid sodium morrhuate (q.v.), has been introduced as a sclerosing agent. The official pharmaceuticals include only those which are intended for internal administration.

OFFICIAL OCCURRENCE	PER CENT COD LIVER OIL
U.S.P.	
Cod Liver Oil Emulsion.....	50.0
N.F.	
Cod Liver Oil with Malt.....	30.0

Corn Oil U.S.P. is "the refined fixed oil expressed from the embryo of *Zea mays* Linné (Fam. *Graminae*).¹" It is a semi-drying oil. Use is made of corn oil as a solvent for vitamins and for injections of oil-soluble medicaments such as estrogenic substances, menadion and diethylstilbestrol.

Cottonseed Oil U.S.P. "is the refined fixed oil obtained from the seed of cultivated plants of various varieties of *Gossypium hirsutum* Linné or of other species of *Gossypium* (Fam. *Malvaceae*).¹" It is a liquid containing the glycerides olein and linolein. Exposure to air causes the unsaturated glycerides to be oxidized, thus causing the development of a gummy substance.

OFFICIAL OCCURRENCE	PER CENT COTTONSEED OIL
U.S.P.	
Camphor Liniment	80.0
N.F.	
Compound Tar Ointment	34.0
Zinc Compounds and Eugenol Cement	15.0

Sesame Oil (Teel Oil, Benne Oil) N.F.

"is a fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* Linné (Fam. *Pedaliaceae*). It contains about 75 per cent olein, with some linolein, palmitin, stearin and myristin. It is classified as a "semi-drying" oil. Sesame oil is used as an emollient, as a food and as a solvent. Lipiodine Diagnostic N.N.R. is a 60 per cent solution of lipiodine in sesame oil.

OFFICIAL OCCURRENCE	PER CENT SESAME OIL
N.F.	
Ammonia Liniment	74.0

Halibut Liver Oil U.S.P. "is the fixed oil obtained from the fresh, or suitably preserved livers of *Hippoglossus hippoglossus* Linné (Fam. *Pleuronectidae*). Like cod liver oil, it contains vitamins A and D, and therefore has nutritional uses.

The average dose is 0.1 cc.

Linseed Oil (Flaxseed Oil, Raw Linseed Oil) N.F. "is the fixed oil obtained from the dried ripe seed of *Linum usitatissimum* Linné (Fam. *Linaceae*). It is one of the principal "drying" oils. To increase its ability to absorb oxygen (its "drying" property), the oil is treated with driers such as litharge, red lead and manganese dioxide. The U.S.P. stipulates that "boiled" linseed oil must not be used or dispensed. The high percentage of unsaturated fatty acid residues, such as linolenic and linoleic, make it useful in paints and varnish.

OFFICIAL OCCURRENCE	PER CENT LINSEED OIL
N.F.	
Lime Liniment	50.0
Compound Rosin Cerate.....	13.0
Zinc Oxide Soft Paste.....	25.0

Expressed Almond Oil (Sweet Almond

Oil) U.S.P. "is the fixed oil obtained from the kernels of varieties of *Prunus amygdalus* Botsch (Fam. *Rosaceae*). It is a "non-drying" oil composed mainly of olein, with some linolein, but no stearin, present. The oil is free from odor and taste and has no tendency to become gummy. It is used as an emollient and as an emulsifier of volatile oils.

The average dose is 4 to 30 cc.

OFFICIAL OCCURRENCE	PER CENT EXPRESSED ALMOND OIL
U.S.P.	
Rose Water Ointment.....	56.0

Peanut Oil (Arachis Oil) U.S.P. "is the fixed oil obtained by cold pressure from the peeled seeds of one or more of the cultivated varieties of *Arachis hypogaea* Linné (Fam. *Leguminosae*). It is a "nondrying" oil containing olein, linolein, arachiden and lignocerin. In pharmaceutical uses it is similar to olive oil. One recent application is a mixture of wax and peanut oil as a vehicle for penicillin.

Coconut Oil N.F. "is the fixed oil obtained by expression or extraction from the kernels of the seeds of *Cocos nucifera* Linné (Fam. *Palmae*). This oil is really a fat since its melting point is 28° to 30° C. and it is a solid at room temperature. Besides the glycerides palmitin, stearin and olein, coconut oil contains about 50 per cent of laurin and smaller amounts of myristin, caprin, caprylin and caproin.

Coconut oil is useful in soap manufacture, as the soaps of the acids of low molecular weight are more soluble in water and less affected by the presence of electrolytes. In ointments, it increases the ability to take up water and makes the product more readily absorbed by the skin.

Persic Oil (Apricot Kernel Oil, Peach Kernel Oil) U.S.P. "is the oil expressed from the kernels of varieties of *Prunus Armeniaca* Linné (Apricot Kernel Oil), or from the kernels of varieties of *Prunus Persica* Sieb. et Zucc. (Peach Kernel Oil). (Fam. *Rosaceae*). In physical and chemical properties it is very similar to expressed

oil of almond. Persic oil has the same uses as almond oil.

Iodized Oil U.S.P. is "an iodine addition product of vegetable oils, containing not less than 38 per cent and not more than 42 per cent of organically combined iodine (I)." Any vegetable oil may be used. The presence of double bonds in a glyceride is, of course, essential. Iodine addition causes the oil to become more viscous, or thick, so that, in order to produce a more fluid iodized oil, the vegetable oil selected is usually a "semi-drying" oil that is moderately high in unsaturated glycerides. Ethyl oleate may be added to a viscous oil to make it more fluid. Long standing and exposure to air or sunlight causes iodized oil to decompose and darken, rendering it unfit for use. Most of the iodized oils and fatty acids are employed as a contrast medium in roentgenography and as a substitute for inorganic iodides. Taken internally, they pass unchanged through the stomach into the intestine, where they are saponified and absorbed in the normal metabolic manner. In the lipoid tissues, where the iodized fatty acid is deposited, a slow breakdown occurs and this liberates iodine as iodide ions into the blood stream.

Lipiodol N.N.R. is an iodine addition product of poppy seed oil that contains 40 per cent iodine in organic combination. It is used as a substitute for inorganic iodides and as a contrast medium in roentgenography.

Lipiodol Radiologique Ascendant N.N.R. is an iodine addition product of poppy-seed oil, containing 9.8 to 11.2 per cent of iodine in organic combination. This iodized oil is a contrast media in the diagnosis of intradural tumors. Its density is less than that of the spinal fluid.

Iodochloral is peanut oil having 27 per cent iodine and 7.5 per cent chlorine in organic combination. It has the same applications as iodized oil and is claimed to have the advantage of greater stability.

ESTERS OF INORGANIC ACIDS

Inorganic acids, like organic acids, will form esters with an alcohol. Pharmaceutically, the important ones are the bromide, chloride, nitrite and nitrate. The chlorides and bromides are conventionally thought of as chloro- or bromo- compounds and they are discussed with that type of compounds. Hydrogen cyanide forms the organic cyanides or nitriles ($R-CN$). Sulfuric acid forms organic sulfates, of which methyl sulfate and ethyl sulfate are the most common. These two are employed in organic synthesis. (For other sulfates, see surface-active agents.)

Ethyl Nitrite, C_2H_5ONO , is readily prepared from ethyl alcohol and nitrous acid; however, the oxides of nitrogen are usually used in commercial production. The ester boils at $17^\circ C$. and is a gas at room temperature. It is supplied commercially dissolved in alcohol in ampules. An alcohol solution of approximately 4 per cent is official as Spirit of Ethyl Nitrite N.F. The spirit should be placed in small containers and stored in a dark, cool place. At best, the product will slowly decompose and should be protected from moisture, heat and light.

The organic nitrites or nitrates and the inorganic nitrites are vasodilators and are useful in treating angina pectoris, hypertension, asthma, gastro-intestinal spasm and certain cases of migraine.

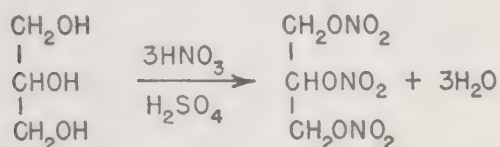
OFFICIAL OCCURRENCE	PER CENT ETHYL NITRITE
N.F.	
Compound Opium and Glycyrrhiza Mixture	Trace

Amyl Nitrite U.S.P. (Isoamyl Nitrite). Amyl nitrite [$(CH_3)_2CHCH_2CH_2ONO$], is a mixture of isomeric amyl nitrites, but is principally isoamyl nitrite. It is official in 90 per cent strength and may be prepared from amyl alcohol and nitrous acid by several procedures. It is usually dispensed in ampule form and used by inhalation, or orally in alcohol solution, for the same purposes as is ethyl nitrite.

Amyl nitrite is a yellowish liquid having an ethereal odor and a pungent taste. At room temperature it is volatile and inflammable. It is nearly insoluble in water, but is miscible with organic solvents. The nitrite will also decompose into valeric acid and nitric acid.

The average dose is 0.2 to 0.3 cc.

Glyceryl Trinitrate (Nitroglycerin, Glonoin, Trinitrin) is the trinitrate ester of glycerol and is official in the form of tablets in the U.S.P. and as a spirit in the N.F. It is prepared by carefully adding glycerin to a mixture of nitric and fuming sulfuric acids. This reaction is exothermic and the reaction mixture must be cooled to 10° to 20° C.



The ester is a colorless oil with a sweet, burning taste. It is only slightly soluble in water, but it is soluble in organic solvents.

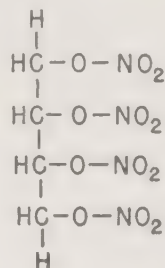
Nitroglycerin is used extensively as an explosive in the form of dynamite. The spirit, if allowed to evaporate or if spilled, will leave a residue of nitroglycerin. To prevent an explosion, the ester must be decomposed by the addition of alkali. It has a strong vasodilating action and, since it is absorbed through the skin, is prone to cause headaches among workers associated with its manufacture. In medicine, it has the typical action of nitrites and is used as are ethyl and amyl nitrite, although its action is more slowly developed and is of longer duration.

The average dose is 0.4 mg.

OFFICIAL OCCURRENCE	PER CENT GLYCERYL TRINITRATE
N.F.	
Glyceryl Trinitrate Spirit . .	1.0

Erythrityl Tetranitrate (Erythrol Tetranitrate, Tetranitrol) is official as tablets in the U.S.P. It is the tetranitrate ester of erythritol and nitric acid and it is prepared in a manner analogous to that used for nitro-

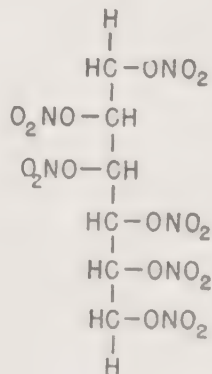
glycerin. The result is a solid, crystalline material. This ester also is very explosive; it is slightly soluble in water and is soluble in organic solvents.



Erythrityl tetranitrate is an organic nitrate, just as is nitroglycerin, but it requires slightly more time to develop its action and this is of longer duration. These organic nitrates are reduced by the body to nitrites and thus exhibit the same physiologic response as ethyl and amyl nitrites. The time required for this reduction may be the cause of the delayed action. All are vasodilators and appear to lessen the tone of arterial muscle, in this way producing a prompt fall of blood pressure. Erythrityl tetranitrate is useful where a mild, gradual and prolonged vascular dilation is wanted. It is used in the treatment of, and as a prophylaxis against, attacks of angina pectoris and to reduce blood pressure in arterial hypertonia.

The average dose is 30 mg.

Mannitol Hexanitrate (Mannitol Nitrate, Nitromannite) N.N.R. is prepared by the nitration of mannitol. It, too, is an explosive compound and is used in medicine diluted with nine parts of a carbohydrate.



It has physiologic properties and uses similar to those of glyceryl trinitrate and erythrityl tetranitrate. Table 13 gives the relation between these inorganic esters and sodium nitrite as to speed of action and duration.

2. Keeney, E. L.: Bull. Johns Hopkins Hospital 73:379 & 479, 1943.
3. Warshaw, L. J., and Gold, H. J.: Am. Pharm. A. 36:56, 1947.
4. von Loesecke, H. W.: J. Ind. Eng. Chem. (Ind. Ed.) 23:1952, 1945.

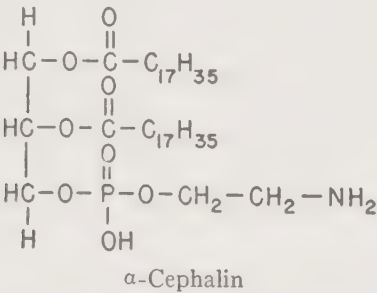
TABLE 13. RELATION BETWEEN SPEED AND DURATION OF ACTION OF SODIUM NITRITE AND CERTAIN INORGANIC ESTERS

COMPOUND	ACTION BEGINS (MINUTES)	MAXIMUM EFFECT (IN MINUTES)	DURATION OF ACTION (IN MINUTES)
Amyl Nitrite	1	3	7
Glyceryl Trinitrate	2	8	30
Sodium Nitrite	10	25	60
Erythrityl Tetranitrate	15	32	180
Mannitol Hexanitrate	15	70	300

The average dose is 15 to 30 mg.

Brain Lipoid (Impure Cephalin, Impure Kephalin) N.N.R. is an extract of the brain of the ox or other animals. The preparation is useful in supplying the "thromboplastic substance" or "thromboplastin" necessary to promote blood coagulation. The extract contains a mixture of compounds known as "cephalins."

5. Keeney, E. L.: *et al.*: Bull. Johns Hopkins Hospital 75:417 & 377, 1944.
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10

Aliphatic Nitrogen-Containing Compounds

AMINES
CYANIDES

AMIDES
NITRO AND NITROSO COMPOUNDS

AMINES

All of the organic nitrogenous compounds may be considered as derived from ammonia by substitution of hydrogen. The amines are formed by replacing hydrogen with alkyl radicals and, because there are three atoms of hydrogen, successive substitution yields three kinds of compounds: primary, $R-NH_2$; secondary, R_2NH and tertiary, R_3N , amines. Each of these behaves chemically like ammonia in adding acids to form salts that are similar to ammonium salts; using HA for the acid, there are

$R-NH_3A$, R_2NH_2A , and R_3NHA . Similarly, there are compounds analogous to ammonium hydroxide: $R-NH_3OH$, R_2NH_2OH and R_3NHOH . Finally, there are two more classes of compounds that are formed by replacing the last hydrogen of ammonium salts and ammonium hydroxide: R_4NA and R_4NOH .

These eleven types are named as derivatives of ammonia (amine) and ammonium compounds. Using methyl as the alkyl and Cl as the acid radical, the following compounds are possible.

PRIMARY

$R-NH_2$	CH_3-NH_2	Methylamine
$R-NH_3Cl$	CH_3-NH_3Cl	Methylammonium chloride
$R-NH_3OH$	CH_3-NH_3OH	Methylammonium hydroxide

SECONDARY

R_2NH	$(CH_3)_2NH$	Dimethylamine
R_2NH_2Cl	$(CH_3)_2NH_2Cl$	Dimethylammonium chloride
R_2NH_2OH	$(CH_3)_2NH_2OH$	Dimethylammonium hydroxide

TERTIARY

R_3N	$(CH_3)_3N$	Trimethylamine
R_3NHCl	$(CH_3)_3NHCl$	Trimethylammonium chloride
R_3NHOH	$(CH_3)_3NHOH$	Trimethylammonium hydroxide

QUATERNARY

R_4NCl	$(CH_3)_4NCl$	Tetramethylammonium chloride
R_4NOH	$(CH_3)_4NOH$	Tetramethylammonium hydroxide

In more complicated amines, the salts often are designated as hydrochlorides, sulfates, nitrates, etc. Thus, $(\text{CH}_3)_3\text{NHCl}$ would be trimethylamine hydrochloride and might then be written $(\text{CH}_3)_3\text{N.HCl}$.

In the Geneva system, the primary group ($-\text{NH}_2$) is expressed by the prefix amino-, using the appropriate number. The simple alkyl derivatives are called alkylamino- or dialkylamino- compounds. Thus, *n*-butylamine would become 1-aminobutane, while nonyldimethylamine would be 1-dimethylaminononane. The number, in each case, denotes the position of the amino group on the parent compound.

The actual structure of these compounds should be noted at this point. In the primary, secondary and tertiary amines, as in ammonia, three of the surface electrons are shared; dimethylamine, for example, could

be pictured as $\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 : \ddot{\text{N}} : \\ | \\ \text{H} \end{array}$. This leaves two of

the five outer electrons free to be transferred in a polar way or to be shared in the covalent way. When an acid is added to form a salt, the hydrogen ion is probably combined to produce an ammonium ion, such

as $\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 : \ddot{\text{N}} : \text{H}^+ \\ | \\ \text{H} \end{array}$; when water is added to

produce the hydroxide, there is a similar process but the hydroxyl ion is probably associated through a hydrogen bond. Thus, a real picture of such a quaternary amine as $(\text{CH}_3)_4\text{NCl}$ would be $(\text{CH}_3)_4\text{N}^+ \text{Cl}^-$, just as a real picture of sodium chloride would be $\text{Na}^+ \text{Cl}^-$ and not NaCl , as it is usually written. Some chemists have a tendency to indicate in formulas the electrons and ionic charges, but most authors prefer to write those of the amines in the customary way.

The primary, secondary and tertiary alkylamines are all colorless, the lower ones being gases and the higher ones liquids or solids. Most of them will dissolve readily

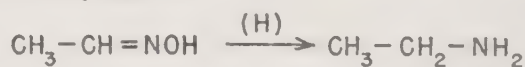
in water, even with alkyl groups having as many as nine carbon atoms, and they are also soluble in alcohol. The more volatile alkylamines have an ammoniacal and fishy odor and, unlike ammonia, are inflammable. The quaternary salts are crystalline solids, and the quaternary hydroxides are usually hygroscopic solids.

PREPARATION

There are many methods for producing the simple amines, and some of these will be noted under particular compounds. At this point, only a few of the methods that are generally applicable will be noted.

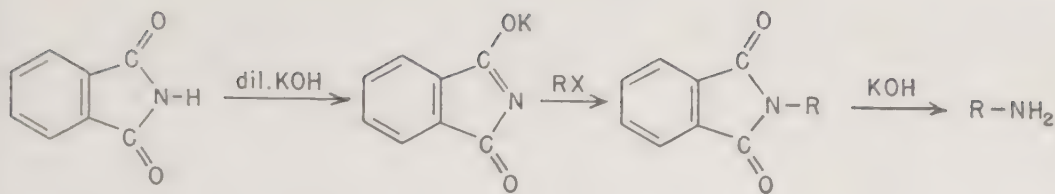
1. **ALKYLATION.** All classes may be made by the process of alkylation, which will be described under the chemical properties.

2. **REDUCTION.** The primary and secondary amines can be made by reducing a great variety of other nitrogenous compounds; indeed, the end product of such a reaction is almost invariably an amine, no matter what substance is used. The most useful compounds for the purpose are nitro and nitroso derivatives, nitriles, oximes, carbylamines and amides. Thus, acetaldoxime gives ethylamine.



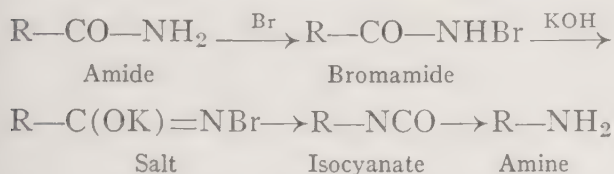
The reducing agent to be used will depend somewhat upon the substance that is to be affected, but usually the more powerful reducing agents are better because the process cannot very well be carried too far. For example, the nitroparaffins can be changed to alkylamines by zinc and dilute acid.

3. **GABRIEL'S METHOD.** This is an excellent method for preparing primary amines. Phthalimide (q.v.) contains a hydrogen atom that is replaceable by potassium or sodium, and the resulting compound will react with alkyl halides to form monoalkyl derivatives of phthalimide. The latter may be hydrolyzed to furnish an amine and a phthalate.



A similar method starts with *p*-nitrosoamines of benzene; *p*-nitrosodimethylaniline decomposes to dimethylamine on heating with alkali.

4. **HOFMANN DEGRADATION.** The primary amines may be prepared by the action of alkaline hypobromites on primary amides in the Hofmann degradation. The end product from $\text{R}-\text{CO}-\text{NH}_2$ is $\text{R}-\text{NH}_2$, but the process takes place in four steps. This is shown, using the potassium salt.



The bromamide and the isocyanate can both be isolated under special conditions. When the radical contains too many carbon atoms, usually above four, the final product tends to be a nitrile of the next lower acid. Thus, $\text{R}-\text{CH}_2-\text{CO}-\text{NH}_2$ may produce largely $\text{R}-\text{CN}$ instead of $\text{R}-\text{CH}_2-\text{NH}_2$. However, the nitrile subsequently can be reduced to the latter and so give the same end product. The isocyanates, which are intermediate in this process, and also the isothiocyanates, can be changed directly to primary amines by heating with alkalies.

5. **DECARBOXYLATION.** Amino acids or alkyl derivatives generally can be decarboxylated by heating with barium hydroxide or by the aid of certain micro-organisms or enzymes. Thus, $\text{R}-\text{CH}(\text{NH}_2)-\text{COOH}$ by such a process gives $\text{R}-\text{CH}_2-\text{NH}_2$.

Many other methods have been described, some of them involving considerable rearrangement, but those that have been noted are the most commonly used. Industrially,

several special processes are employed; as examples, the methylamines can be made by heating formaldehyde with alkali and ammonium chloride, and lower alcohols can be converted to primary amines by heating with ammonium chloride and alkali under pressure.

PROPERTIES

In general, the alkylamines are entirely analogous to ammonia in their chemical behavior, although there may be considerable differences in degree under certain conditions. For instance, most of the lower amines are inflammable, while ammonia can be burned only under unusual circumstances. Most of them combine with water to form oily hydrates analogous to ammonium hydroxide, which exists in small amount in solution or in the pure state at low temperature. These hydrates can be decomposed by reaction with strong bases to produce the free amine.

1. Like ammonia, the amines unite directly with acids to form salts. The alkalinity of aqueous solutions is higher than that of ammonia and sometimes increases with the number of alkyl groups. Quaternary ammonium bases are equivalent in strength to the strong alkalies because they contain no hydrogen to lessen the activity of the hydroxyl ion by hydrogen bonding and will absorb carbon dioxide to form carbonates. The basic properties of any amine in aqueous solution are shown by its ability to precipitate metallic hydroxides and, in excess, to dissolve many of them as does ammonia. Table 14 shows the ionization constants and boiling points of a few of the lower amines.

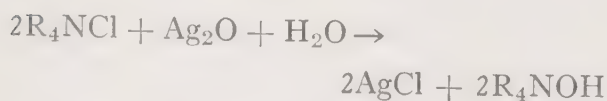
TABLE 14. IONIZATION CONSTANTS AND
BOILING POINTS OF CERTAIN
LOWER AMINES

PRIMARY AMINES	$K \times 10^{-4}$ at 25° C.	BOILING POINT (° C.)
Ammonia	0.18	—33.5
Methylamine	5.0	— 6.7
Ethylamine	5.6	19.0
Propylamine	4.7	50.0
Isopropylamine	5.3	33.0
Butylamine	..	77.8
Isobutylamine	3.1	68.0
s-Butylamine	4.4	63.0
t-Butylamine	3.4	45.2
Amylamine	..	104.0
Isoamylamine	5.0	95.0

SECONDARY AMINES	$K \times 10^{-4}$ at 25° C.	BOILING POINT (° C.)
Dimethylamine	7.4	7.2
Ethylmethylamine	..	34.0
Diethylamine	12.6	56.0
Methylpropylamine	..	63.0
Ethylpropylamine	..	80.0
Ethylisopropylamine	..	76.0
Dipropylamine	10.2	110.0

TERTIARY AMINES	$K \times 10^{-4}$ at 25° C.	BOILING POINT (° C.)
Trimethylamine	0.7	3.5
Ethyltrimethylamine	..	29.0
Diethylmethylamine	2.7	66.0
Triethylamine	6.4	89.0
Tripropylamine	5.5	156.5

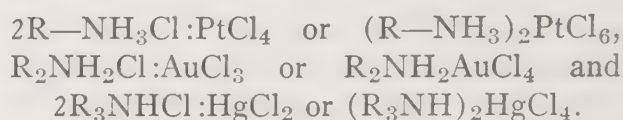
The salts that are formed by the addition of acids are colorless, crystalline solids that are generally soluble in water or alcohol and, like other salts, are highly ionized. From them, the bases may be liberated by addition of alkalies. The quaternary salts, however, are not so altered because the corresponding bases are about as strong as the reagents. In these cases, the bases may be produced by shaking the salts with moist silver oxide, forming an insoluble silver salt.



Any one of the alkyl amino halide salts is decomposed into alkyl halide and an amine when heated. Thus, dimethylammonium

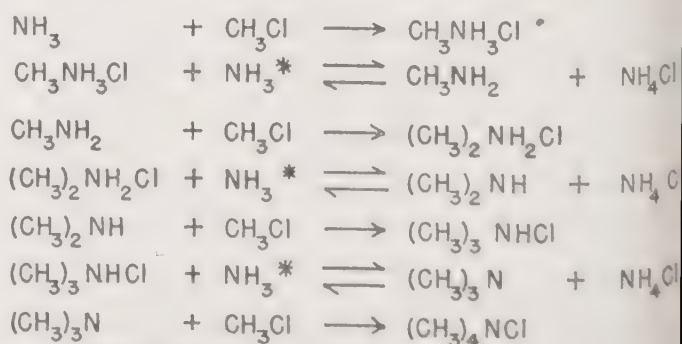
chloride produces methylamine and methyl chloride, a reversal of the process of alkylation. In the same way, the quaternary bases will give a tertiary amine and an alcohol. If the radicals are different in the substance being heated, the alcohol or alkyl halide that is split out will generally contain the smallest alkyl group.

All of the salts can combine, as do those of ammonium, with various metallic salts to form double compounds. Examples of these are:



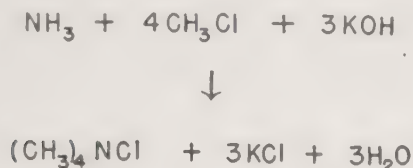
2. When ammonia or any simple amine is heated with an inorganic alkyl ester, union takes place to produce a salt of an amine with one more alkyl group. As an example, $R-NH_2$ will give $R-N(CH_3)-H_2I$ with methyl iodide, and methylamine is converted to $(CH_3)_2NH_2I$. For this purpose, alkyl halides or sulfates are most convenient, but it is noteworthy that compounds of tertiary radicals do not add, they produce olefines instead. Since the process of addition is usually performed in order to introduce alkyl radicals into the amine in place of hydrogen, it is called alkylation (methylation, ethylation, etc.).

Unfortunately, however, the reaction is not quite so simple as noted. The ammonium salt that is formed can be converted by bases to the free amine, as has already been mentioned, and all amines are bases. Therefore, while the addition is more or less



* Any other amine in the system will also react.

complete, other reactions go on in equilibrium, so that the final result is to form a conglomerate mixture of compounds. If ammonia is heated with methyl chloride, for example, the foregoing mixture would result. On the other hand, if a strong base is added to the reaction mixture, the equilibrium processes are carried completely to the right and the final product is a quaternary salt.

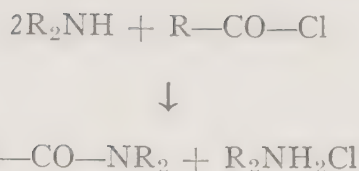
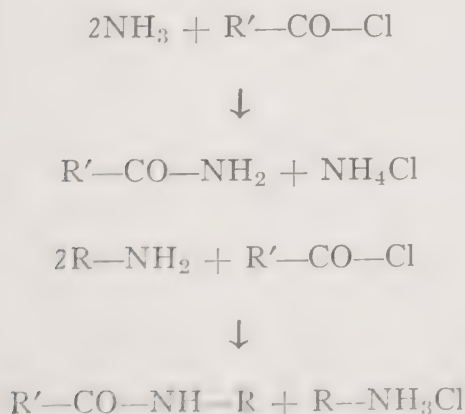


From this, the tertiary compound may be obtained by distillation.



Therefore, this alkylation can be employed to prepare tertiary amines, quaternary salts, or from the latter, the corresponding bases, but that it is not usually efficient for producing the primary or secondary compounds. Under special circumstances and by carefully controlling conditions, it is sometimes possible to get primary or secondary amines in more or less pure form, but in general, this is not a good method for preparing them.

3. Acylating agents react with the hydrogen of amines to form amides. Such a reaction with the acid is slow and unsatisfactory in some cases, but either the anhydride or chloride is more rapid and more convenient.

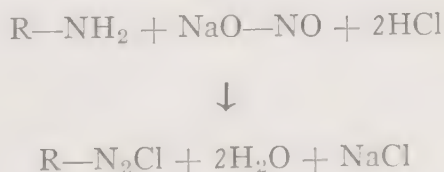


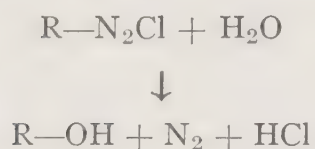
The agents that are applicable may include the halides of nonmetals or of inorganic acids, such as the chlorides of thionyl, sulfur, phosphorus, sulfur or nitrosyl.

An interesting modification of this process was proposed by Hofmann to distinguish and separate the various classes of amines. When these are treated with ethyl oxalate, the primary forms a dialkylamide, R—NH—CO—CO—NH—R , that is soluble in water, and from it the amine can be recovered by distillation with alkali. The secondary compound forms an insoluble dialkylamide ester, $\text{CH}_3\text{—CH}_2\text{—O—CO—CO—NR}_2$, from which the amine can be released by heating with alkali. The unaltered tertiary compound can first be removed by simple distillation.

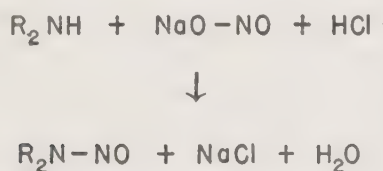
Another means of distinguishing the amines is by reaction with carbon disulfide in alcoholic solution. Primary amines add to yield salts of alkylthiocarbamic acid, R—NH—CS—S—NH_2 , while the secondary amine gives dialkylthiocarbamic acid salts, $\text{R}_2\text{N—CS—S—NH}_2$. After distilling off the unchanged tertiary amine, the residue is boiled with mercuric or ferric chloride, when the primary compound is converted to a mustard oil, RNCS .

4. One reaction that is very useful, especially for the primary amine, is that brought about by a metallic nitrite and a dilute mineral acid, essentially a reaction of nitrous acid. At room temperature the primary compound is converted to an alcohol, probably through an intermediate diazonium salt.



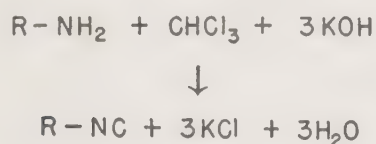


This provides a convenient method for transforming the group —NH_2 to the alcoholic —OH . The secondary amine is changed to a nitrosamine by condensation.



The nitrosamines are oily, yellow liquids that are insoluble in water, stable to heat or reagents generally, but reducible to hydrazines. Tertiary amines are unchanged by the nitrous acid but are converted to salts of the acid that is used.

5. Primary amines will form isocyanides or carbylamines when boiled with chloroform and alcoholic alkali.



These are poisonous, ill-smelling liquids; the characteristic odor may be used to identify the presence of a primary amine.

USE IN PHARMACY

The amines with low molecular weight are similar to ammonia in physiologic as well as chemical properties. They undoubtedly have a profound effect in the animal body, but since the irritant action far outweighs any possible other effect, they are useless as drugs. The salts are readily hydrolyzed to the amines, as are the salts of ammonia, but they would have no great advantage over the latter in producing osmosis and systemic acidity. Trimethylamine and its salts have been administered in rheumatic conditions on the doubt-

ful basis that they tend to dissolve urate deposits, and unsuccessful efforts have been made to apply other lower members of the series. Some of them, notably the methyl compounds, are useful in synthesis and otherwise in industry. Those amines with higher molecular weight are less volatile and less irritant and might be employed to give more useful effects in medicine; this is particularly true of those containing other substituents, such as derivatives of choline. These applications will be noted under the individual compounds.

Tuamine (Racemic 2-Aminoheptane) N.N.R. occurs as a colorless to pale yellow liquid that boils at 138 to 142° C. It is sparingly soluble in water but is freely soluble in common organic solvents. The pH of a 1 per cent aqueous solution is about 11.45.

Tuamine produces a local vasoconstrictive action similar to that of other sympathomimetic drugs. It is used in the form of the carbonate by inhalation for treatment of acute rhinologic conditions, particularly when prolonged or repeated medication is necessary. In cases of cardiovascular disease it should be employed with caution.

Tuamine Sulfate N.N.R. is a white, odorless powder that is readily soluble in water. It is said to give equal vasoconstrictive effects when used in about one-half of the effective concentration of ephedrine, and the duration of action is longer. A 1 per cent solution is generally adequate when applied by spray, dropper or tampon, while a 2 per cent solution may be used for operative procedures, diagnostic examination or under special circumstances. The solution is buffered with primary potassium phosphate and preserved with a mixture of methylparaben and propylparaben.

Methylaminoheptane (Oenethyl), a clear, colorless, volatile liquid that is sparingly soluble in water, is the methyl derivative of tuamine, 2-methylaminoheptane. The hydrochloride has been recommended in cases of hypotension under spinal anesthesia.¹ Intramuscular doses of 0.075 to 0.1

gram give a pressor effect in 2 to 5 minutes, but 0.01 to 0.05 gram intravenously, in divided doses every minute or so, appears to be safer.

Octin, 6-methylamino-2-methylheptene, is a colorless liquid that has a characteristic odor; it is insoluble in water but is freely soluble in alcohol. It is used² like ephedrine, generally in the form of hydrochloride or mucate, and is recommended in the treatment of vesical or ureteral spasms, spastic dysmenorrhea or other similar conditions. The dose is 0.1 gram intramuscularly or slightly larger amounts orally in the form of tablets or a 10 per cent solution.

Another compound that is employed in the same condition is Cyverine Hydrochloride, methylbis- β -cyclohexylethylamine hydrochloride. Pharmacologic tests seem to show that it is not very reliable.

Nitrogen Mustards or chloroethylamines, analogous to mustard gas and prepared originally for possible use in chemical warfare, were found to have potential value in destroying neoplasms by a mechanism as yet unknown. The compounds so far most used are methylbis- β -chloroethylamine (Methylbis), $\text{CH}_3\text{—N}(\text{CH}_2\text{—CH}_2\text{Cl})_2$, and tris- β -chloroethylamine, $(\text{CH}_2\text{—CH}_2\text{Cl})_3\text{N}$. The systemic effect is a selective destruction of actively proliferating cells, and this results in the dissolution of tumors in experimental neoplasms. The hydrochlorides have been used³ in Hodgkin's disease, leukemia and lymphosarcoma with very promising improvements. They are administered by a special intravenous technic to avoid extravasation of the solution and to prevent it from coming in contact with the mucous membranes or the skin of the patient or operator. Thrombophlebitis of the vein has been encountered, and nausea and vomiting some time after injection seem to be unavoidable, although deep sedation of the patient can be used to counteract them. The dose given has been 0.1 milligram per kilogram, but never over 8 milligrams at a single injection, and these have been given daily or every other day for 3 to 6 doses, then

no further treatment for from 6 to 8 weeks. Because the salts are hydrolyzed rapidly the solutions must be prepared freshly.

Tetraethylammonium Bromide (TEAB) and Tetraethylammonium Chloride (Etamon Chloride) were introduced to produce blockade of the autonomic ganglia, both sympathetic and parasympathetic, obliterating vasoconstrictive tone. This action of the tetraethylammonium ion was first observed by Burn and Dale⁴ in 1915, but only recently have the compounds been made available. The action is comparatively short, because 50 per cent is found in the urine in 30 minutes after intravenous injection and nearly all of it in 24 hours. After intramuscular injection, 50 per cent appears in the urine in 3 hours; absorption from the gastro-intestinal tract is very poor, only about 6 to 15 per cent appearing in the urine. No major toxic manifestations have been observed, but single injections sometimes cause some peripheral vascular collapse, weakness and muscular tremors; repeated injections over two days may cause discomfort, such as dry mouth and inability to void, eat or stand. The compounds interrupt normal transmission of nerve impulses and, by so doing, aid in relaxing nerve-induced constriction of peripheral blood vessels, thus tending to re-establish blood flow in diseases involving restricted circulation in the extremities. They are recommended to relieve such vasoconstrictive states as Raynaud's syndrome and peripheral embolism, to relieve pain associated with excessive peristalsis and in causalgia, to aid in the selection of patients suitable for sympathectomy, and to ease the acute manifestations of hypertension.

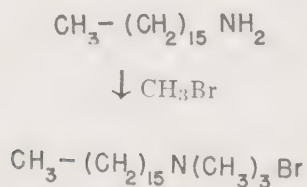
Triethanolamine U.S.P. is a mixture consisting largely of triethanolamine, $\text{N}(\text{CH}_2\text{—CH}_2\text{OH})_3$, with smaller amounts of the primary and secondary compounds, $\text{NH}_2\text{—CH}_2\text{—CH}_2\text{OH}$ and $\text{NH}(\text{CH}_2\text{—CH}_2\text{OH})_2$ respectively. It is manufactured by the action of ammonia on ethylene oxide (q.v.). "It has an alkalinity equivalent to not less

than 6.7 cc. and not more than 7.2 cc. of normal acid for each Gm. of Triethanolamine." The substance is a colorless to pale yellow, viscous, hygroscopic liquid having a slightly ammoniacal odor. It is miscible with water or alcohol and is soluble in chloroform.

Triethanolamine is an excellent emulsifying agent in the preparation of ointments and creams. It combines with fatty acids to form compounds with good detergent properties, and these are soluble in water and in oils. It is claimed to possess a certain amount of bacteriostatic power.

For the preparation of stable emulsions, the mixture of fatty acid (e.g. oleic) and triethanolamine is added to a portion of the oil, and an equal portion of the water is added while stirring. During continued agitation, the remaining oil and water are added in portions. For vegetable oils, 2.4 per cent of the amine and 11.5 per cent of the acid may be employed, while for paraffin oils, the amount of triethanolamine should be increased to 5 per cent. Emulsions so made with 20 to 40 per cent of oil may be diluted with as much as five times the volume of water.

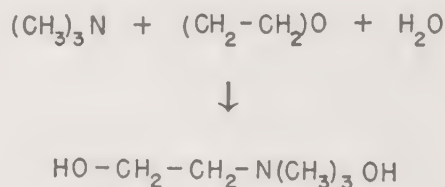
Cetavlon (CTAB) is one of the cationic type of bactericides, which includes phenmerol, ceepryn and the official benzalkonium chloride. These all involve quaternary ammonium salts, whose anion is immaterial and whose four groups usually include two methyls, a hydrocarbon radical of long chain and an aromatic radical. Cetavlon is made by completely alkylating cetylamine with methyl bromide, and thus it contains methyl in place of an aromatic group.



It is a white powder that has a somewhat astringent and bitter taste and is slightly

soluble in cold water (1:200) but soluble (1:2.5) in warm water. It is recommended especially for washing dirty wounds, since it is a good detergent, but the concentration required for different organisms varies considerably.⁵ It can be used up to 1 per cent without irritation, but much more dilute solutions may be efficacious.

Choline, $\text{HOCH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3\text{OH}$, is also called by many other names such as sincaline, bilineurine, amanitine, gossypine, vidine, bursine, fagine, etc. These testify to its wide occurrence in animals and plants, because they are indicative of source in each case—mustard, bile, mushrooms, cotton, etc. The most useful source is lecithin, which is concentrated in egg yolk and in nerve and brain, which hydrolyzes to fatty acids, glycerin, phosphoric acid and choline. It is usually made synthetically from trimethylamine and either ethylenechlorohydrin or ethylene oxide.

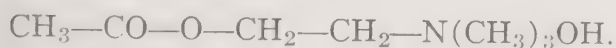


Choline is a colorless, viscid liquid that is very strongly alkaline and absorbs carbon dioxide from the air. It is very soluble in water or alcohol.

Since the discovery that various of its derivatives have a potent action, attempts have been made to use choline as a medicinal agent, although its effects in the same way are very mild. It has been postulated that choline should be of value in hepatic cirrhosis and similar conditions since it is essential in the formation of lecithin from fats and because the administration of lecithin is known to reduce depositions of fat in animal organs. Although methionine, which apparently is a precursor of choline in the body, is claimed to be effective in such circumstances, the results with choline are inconclusive. Furthermore, the administration of choline chloride is not without dan-

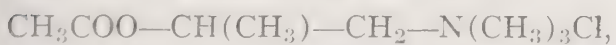
ger, in spite of the fact that oral doses up to 6 grams daily have been given without apparent harm. Although its efficacy in reducing fatty deposits has not been proven, choline is known to be a valuable dietary factor. It is claimed to be particularly useful, for example, in reversing pathologic changes brought about by deficiency of choline through a high intake of cystine.

Acetylcholine,



Acetylcholine is now generally regarded as the intermediary in transmitting nervous impulses at the neuromuscular junctions. Any stimulation liberates a small amount of the compound, which then disappears, probably by the action of the enzyme cholinesterase, as the impulse is sent along the nerve. The duration of action by derivatives of choline may be prolonged by physostigmine, which inhibits the activity of the enzyme. On the basis of this knowledge and of the fact that application of acetylcholine to tissue gives a powerful stimulation of the parasympathetic nerves, attempts have been made to utilize it as a remedy in paroxysmal tachycardia, paralytic ileus, tobacco amblyopia, etc. However, the duration of action is too short for sustained effects and the danger of overdosage is great. The chloride (Acecoline) and bromide (Pragmoline) are available in 0.1 gram ampules, and the chloride has been marketed as a solution in propylene glycol.

Methacholine Chloride (Acetyl- β -methylcholine Chloride) U.S.P. (Mecholyl Chloride). Methacholine chloride,



occurs as colorless or white crystals or as a white, crystalline powder. It is odorless or has a slight odor, and is very deliquescent. It is freely soluble in water, in alcohol or in chloroform, and its aqueous solution is neutral to litmus.

Methacholine may be prepared from trimethylacetonylammonium chloride $(\text{CH}_3)_3\text{NCl—CH}_2\text{—CO—CH}_3$, which is catalyti-

cally reduced in absolute alcoholic solution, using hydrogen with platinum oxide and a trace of ferric chloride. The product then is acetylated by heating with acetic anhydride.

Unlike acetylcholine, the methyl derivative has sufficient stability in the body to give sustained parasympathetic stimulation, and this action is accompanied by little or no "nicotine effect." It exerts a depressant action on the cardiac auricular mechanism which is blocked by quinidine, a stimulation of gastro-intestinal peristalsis and a general vasodilation followed by a fall in blood pressure. All of these effects are intensified and prolonged by physostigmine and neostigmine, which inhibit cholinesterase, but are rapidly and completely blocked by atropine.

Because of its hygroscopic character, the drug is not suitable for oral administration but should be given in solution; the contents of containers must be put into solution immediately on opening. The solutions, which are relatively stable to heat and will keep for at least two or three weeks, may be refrigerated to delay growth of molds.

Methacholine chloride may be administered subcutaneously for paroxysmal auricular tachycardia, although it is inferior to quinidine, for Raynaud's disease, scleroderma, chronic ulcers and vasospastic conditions of the extremities. The first dose should be limited to 10 milligrams to test for tolerance, and this may be increased cautiously to 25 milligrams or higher. Cumulative effects of overdosage may be abolished by 0.6 milligram of atropine sulfate. The drug may be given orally in the same conditions, usually 0.2 to 0.5 gram two or three times a day in milk to disguise the bitter taste. It may be administered by iontophoresis from the positive electrode using 0.2 to 0.5 per cent solutions, the strength and duration of current being the regulator of dosage. The initial treatment usually is limited to from 5 to 10 milliamperes for thirty minutes; subsequent treatments may be up to 25 to 30 milliamperes.

OFFICIAL OCCURRENCE

U.S.P.

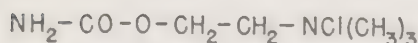
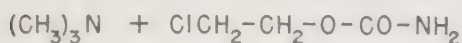
Methacholine Chloride Capsules

Methacholine Chloride Injection

Methacholine Bromide (Mecholyl Bromide) N.N.R. is very similar to the chloride in all of its properties but is somewhat less hygroscopic. For oral use, therefore, it may have an advantage in tablet form, but for injection or ion transfer the chloride is preferable. It is administered in doses of 0.05 to 0.06 gram two or three times daily; the tablets that are available contain 0.2 gram.

Carbachol (Carbamylcholine Chloride) U.S.P. (Doryl, Lentin). Carbachol is a white or faintly yellow, crystalline solid or powder that is odorless and hygroscopic. It is soluble in its own weight of water and in 50 times as much alcohol; the aqueous solution is neutral to litmus paper. It may be prepared by the interaction of trimethylamine with β -chloroethyl carbamate.

It differs from acetylcholine chloride in hav-



ing the carbamyl group in place of the acetyl group.

Carbachol is the most powerful of the parasympathomimetic derivatives of choline. It is less readily absorbed from the gastro-intestinal tract than methacholine, and effects after oral administration are chiefly exerted there. The nicotine effect is somewhat greater and all actions are prolonged, so that carbachol is inclined to be more toxic than the others after injection. Atropine abolishes the muscarinelike effect, but the antidotal action is much slower, and greater doses of atropine are required.

As a remedy, it can be used for the same purposes as others of the class. It is excellent in the pains of peripheral vascular disease of the vasospastic type, for urinary reten-

tion after operation and for abdominal distention due to stasis, and its effects outlast those of other choline derivatives. Because of its toxicity, however, it is usually limited to those cases that do not respond to safer drugs. The dosage by mouth is 0.2 to 0.8 milligram two or three times daily; by subcutaneous injection (never intramuscular or intravenous) the dosage is 0.2 to 0.4 milligram. It is often employed to reduce the intraocular tension of glaucoma when response cannot be obtained with pilocarpine, physostigmine, neostigmine or methacholine. In such cases, a drop of 1.5 per cent solution in benzalkonium chloride (1:3,000) may be instilled at intervals of from 8 to 12 hours.

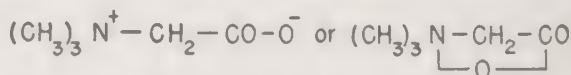
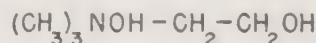
OFFICIAL OCCURRENCE

U.S.P.

Carbachol Tablets

Carbachol Injection

Betaine (Trimethylglycocoll, Oxyneurine, Lysine) is an anhydride of the acid corresponding to choline and can be obtained from the latter by oxidation or from trimethylamine and chloroacetic acid.



It occurs in beetroot, in leaves and stalks of *Lycium barbarum*, in cotton seeds, in the germs of malt and wheat and in young plants generally. It combines with hydrogen chloride, to produce a chloride $(\text{CH}_3)_3\text{-NCl-CH}_2\text{-COOH}$, that easily decomposes to betaine, setting free the hydrogen chloride; it has been administered under the title of Acidol to overcome a deficiency of hydrochloric acid in the stomach.

The name "betaines" has been applied generically to all quaternary salts of amino acids, and this term has also been applied to all internally compensated derivatives of quaternary ammonium, oxonium, sulfonium and other bases of the type.

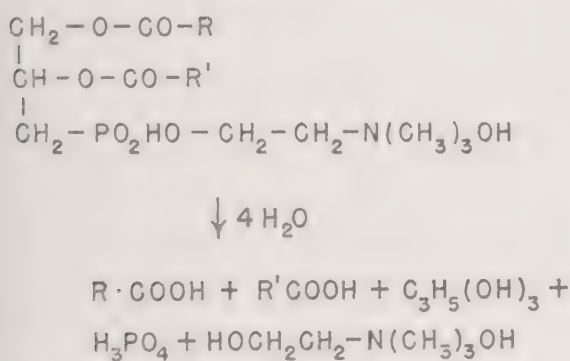
Betaine is apparently a precursor of chol-

ine in plants and gives similar physiologic action in animals, although much milder. It has been used to protect the liver against the effects of diets deficient in choline.

Neurine, $\text{CH}_2=\text{CH}-\text{N}(\text{CH}_3)_3\text{OH}$, is produced whenever choline undergoes putrefaction and, therefore, is often present in small amounts in blood and urine. It can be made in the laboratory by boiling choline chloride with barium hydroxide solution. It is extremely poisonous, giving effects similar to those from muscarine.

Muscarine, the potent substance found in certain poisonous mushrooms, is a similar quaternary base. Although its structure is not known with certainty, it is usually given the formula $(\text{CH}_3)_3\text{NOH}-\text{CH}(\text{CHO})-\text{CHOH}-\text{CH}_2-\text{CH}_3$. In physiologic action it resembles pilocarpine, and its effects are counteracted by atropine.

Lecithins are widely distributed in the animal organism, particularly in the brain, nerves and corpuscles of the blood; they are found also in the yolks of eggs and in the seeds of plants. Upon hydrolysis, lecithins produce a mixture of fatty acids, glycerin, phosphoric acid and choline.



The lecithins obtained from various sources differ somewhat in physical properties, presumably with the identity of the fatty acids and the position of cholinephosphoric acid on the glycerin molecule. The commercial varieties are obtained from eggs or leguminous seeds, particularly from soy beans. They are used in industry as emulsifying agents and as preservatives of food products, especially chocolate.

Lecithins like choline and betaine seem to possess a lipotropic action, i.e., they correct or check abnormalities in lipid metabolism. For example, they will prevent the fatty livers that generally result when depancreatized animals are maintained with insulin and fed diets high in carbohydrates. The crude product from soy beans, containing as much as 30 per cent of oil, is administered by mouth in doses of 3 to 15 grams daily in the treatment of several clinical syndromes. These include sprue, cirrhosis of the liver, hypercholesterolemia of pregnancy, obesity, diabetes, etc., psoriasis, infantile eczema, seborrhea, scleroderma and acne.

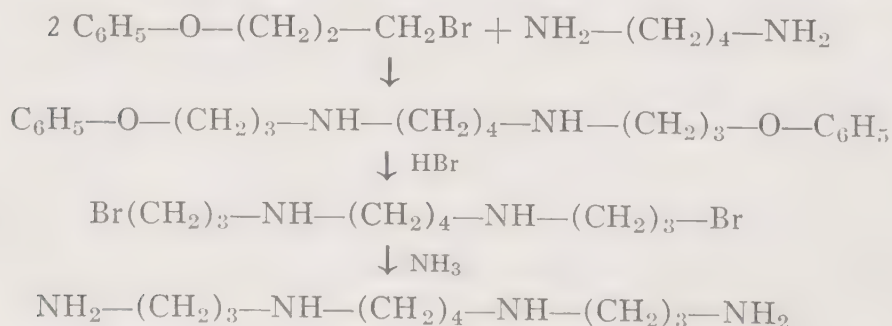
Other phospholipids have been found to be effective only if they contain the labile methyl groups of choline or similar substances. Thus, the lipotropic result can be obtained with sphingomyelins from the brain, the lung, the spleen, the kidney or the liver. These hydrolyze to choline, fatty acids, phosphoric acid and sphingosine or sphingol, which appears to be $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}=\text{CH}-\text{CHOH}-\text{CH}(\text{NH}_2)-\text{CH}_2\text{OH}$. On the other hand, cephalin from brain tissue hydrolyzes to ethanolamine instead of choline and is ineffective. Galactolipids, formerly called cerebrosides or cerebrogalactosides, are found in brain and nerves; they hydrolyze to sphingol, galactose and fatty acids (lignoceric, cerebonic, nervonic), but no choline is produced.

Ethylenediamine Solution U.S.P. "contains not less than 67 per cent and not more than 71 per cent of ethylenediamine ($\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2$). It is a colorless or slightly yellow liquid having an ammonia-like odor and a strongly alkaline reaction: it is miscible with water or alcohol. Ethylenediamine may be prepared from ethylene chloride or bromide by the action of ammonia at elevated temperature and pressure. It is comparatively nontoxic; the minimum fatal dose is more than 0.75 gram per kilogram parenterally.

The solution is official because it is employed to prepare injections of theophylline and to manufacture aminophylline (q. v.). It was at one time suggested as a means for dissolving the pseudomembrane of diphtheria. In industry, it is used in many organic syntheses, to solubilize many acids and for other purposes.

Ethylenediamine hydrochloride has been marketed under the title Chlor-Ethamine as an agent to be administered by mouth for acidifying the urine. The analogous Iod-ethamine has been recommended for therapy with organic iodine, using 0.1 to 1.0 gram several times daily.

Other diamines are of considerable interest, and at least one polyamine is important in biology. Propylenediamine, which is a soluble liquid with an ammoniacal odor, is much like ethylenediamine but is superior as a solvent. Putrescine, 1,4-diaminobutane and cadaverine, 1,5-diaminopentane are substances that are produced by putrefaction of animal and vegetable matter (ptomaines). At one time ptomaines were considered to be poisonous. Both of these may be obtained from amino acids by decarboxylation, the former from ornithine and the latter from lysine. The corresponding derivative of hexane, $\text{NH}_2-(\text{CH}_2)_6-\text{NH}_2$, is used with adipic acid to make Nylon. It is produced from benzene by catalytic oxidation to adipic acid, then treating with ammonia and reducing. Spermine (Geron-tine, Neuridine) occurs as a phosphate in the sperm of man, in the pancreas of oxen, in yeast, etc. It has been synthesized⁶ from phenoxypropyl bromide and putrescine.



AMIDES

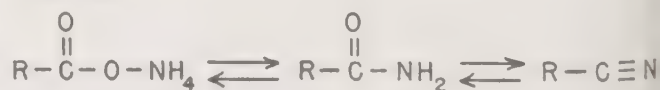
The amides or acid amides are derived from acids by substituting an amino or alkylamino group for the hydroxyl; they also may be regarded as derivatives of ammonia or amines with acyl groups instead of hydrogen. The simple compounds have the formula R—CO—NH_2 , but amides could also be of the types R—CO—NH—R' , $\text{R—CO—NR}'_2$, $(\text{R—CO})_2\text{NH}$ and $(\text{R—CO})_3\text{N}$. The chief point of interest in all such substances is that the nitrogen is connected directly to a carbonyl group, a condition that markedly influences the basic character of the nitrogen and is encountered in many medicinal agents.

The simple or primary amides are named from the corresponding acids. The suffix "ic" and the word "acid" are omitted, and the word "amide" is added as a suffix. Thus, formic acid becomes formamide, and acetic acid becomes acetamide; in the Geneva system, "amide" is added to the root, e.g., ethanoic acid gives ethanamide. In more complicated compounds it seems permissible to append suffixes such as carbonamide, carboxamide or carboxylamide.

PREPARATION

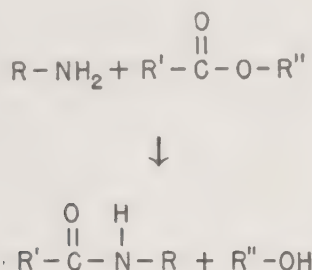
Of the various methods that may be used to prepare amides, the most useful are those given.

1. DRY DISTILLATION. Dry distillation of ammonium salts or of a mixture of sodium salts and ammonium chloride is efficient for some amides, but too often leads mostly to cyanide.



The action is highly reversible and proceeds best if appropriate means are adopted to remove the water as it is formed, an easy task for giving the cyanide but more difficult in case of the amide.

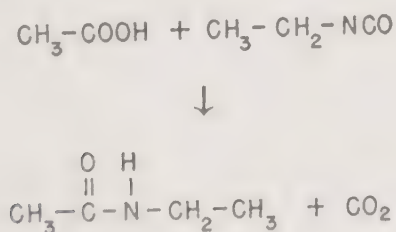
2. ACTION OF AMMONIA OR AMINES ON ESTERS, ACID ANHYDRIDES OR ACID CHLORIDES.



The reaction takes place in the cold, but often requires considerable time and a large excess of the amine. Acetamide, for example, may be made in good yield by mixing ethyl acetate and strong ammonia solution and allowing to digest for at least 24 hours.

3. HYDRATION OF NITRILES. By working under carefully regulated conditions, the primary amides can be prepared by hydration of nitriles. This can sometimes be brought about by mixtures of acids in the cold or by hydrogen peroxide in alkaline solution. If the conditions are not right, ammonium salts may be the products.

4. FROM FATTY ACIDS. They can be obtained by the interaction of fatty acids with potassium thiocyanate, with carbylamines or with alkyl isocyanates. For example, the ethyl derivative of acetamide may be made by treating ethyl isocyanate with acetic acid.



5. ACYLATION. More highly acylated amides may be prepared by using an excess of

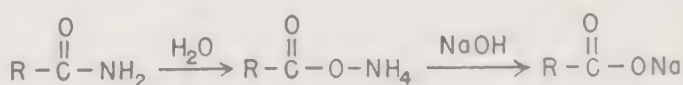
acylating agent or by heating the simple amides with acid anhydrides. Thus, diacetamide, $(\text{CH}_3-\text{CO})_2\text{NH}$, results from the action of excess acetyl chloride on acetamide in benzene solution.

PROPERTIES

The simple amides are usually crystalline solids that are soluble in alcohol or ether, and the lower ones are very soluble in water. They can generally be distilled without decomposition.

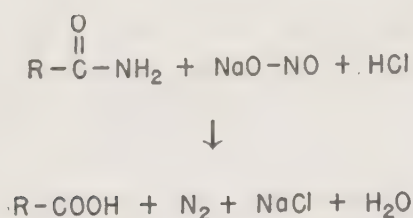
1. The nearness of the negative carbonyl group weakens the basic nitrogen so much that salts with acids are decidedly unstable. Indeed, hydrogen of the amino group is often influenced enough to be acidic in character and capable of being replaced by metals, a condition that is especially pronounced in the alkyl or aryl derivatives or in the diacyl amides. In general, whenever the combination $-\text{CO}-\text{NH}-$ is found, the hydrogen may be replaceable to form fairly stable salts of the type $-\text{CONa}=\text{N}-$; with the grouping $-\text{CO}-\text{NH}-\text{CO}-$, this is certain to be the case, as in the barbitals and hydroxy derivatives of purine. The sulfone group, $-\text{SO}_2-$, has a similar influence on the nitrogen in compounds containing $-\text{SO}_2-\text{NH}-$, as is found in the sulfa drugs.

2. The amides are easily hydrolyzed to ammonia or amine and the acid. Heating with water may accomplish this, but it is performed more easily by boiling with dilute acid or alkali.



On the other hand, dehydration of the primary amide gives the cyanide or nitrile.

3. With metal nitrites and dilute acid, the primary amides produce the acid and nitrogen.



4. Hypobromites act on the primary compounds to give primary amines or cyanides (Hofmann, see p. 119).

USE IN PHARMACY

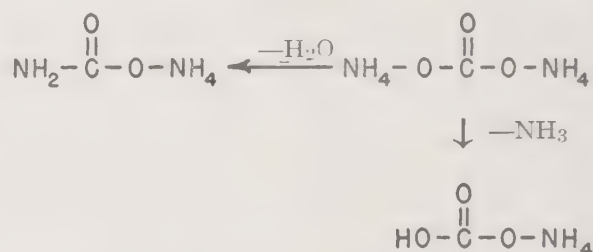
Formamide, $\text{HCO}-\text{NH}_2$, is a thick, colorless liquid that is miscible with water, alcohol or ether. When rapidly heated, it decomposes to carbon monoxide and ammonia, but dehydrating agents produce hydrogen cyanide. It combines with chloral to form chloralformamide, $\text{CCl}_3-\text{CHOH}-\text{NH}-\text{CHO}$, which has been employed as a hypnotic and sedative.

Acetamide, $\text{CH}_3-\text{CO}-\text{NH}_2$, consists of colorless crystals that melt at 82°C . and boil at 222°C . and are very soluble in water or alcohol. It is used as a solvent, plasticizer and stabilizer and to manufacture numerous useful derivatives.

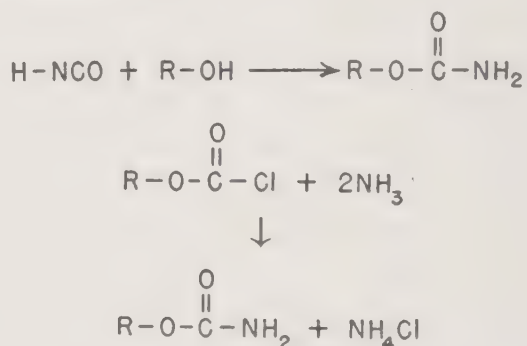
The higher compounds of the acetic acid series have more or less sedative and hypnotic action but are of comparatively minor importance. Among those that have been used in medicine are: isovaleryldiethylamide (Valyl), $(\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{CO}-\text{N}(\text{CH}_2-\text{CH}_3)_2$; bromodiethylacetamide (Neuronal), $(\text{CH}_3-\text{CH}_2)_2\text{CBr}-\text{CO}-\text{NH}_2$; allyldiethylacetamide (Novonal), $\text{CH}_2=\text{CH}-\text{CH}_2-\text{C}(\text{CH}_2-\text{CH}_3)_2\text{CO}-\text{NH}_2$ and α -bromo- α -isopropylbutyramide (Neoderm), $(\text{CH}_3)_2\text{CH}-\text{CBr}(\text{CH}_2-\text{CH}_3)-\text{CO}-\text{NH}_2$. Pellitorine (Pyrethrine), from the root of *Anacyclus pyrethrum* D.C., is an isobutyl substitution product of an undecadienoic amide. A similar isobutylundecylenamide has been marketed as a fly spray. Succinimide, $(\text{CH}_2-\text{CO})_2\text{NH}$, and its derivatives will be considered among the heterocyclic compounds.

Carbamic Acid, NH_2-COOH , although

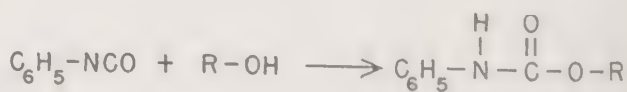
itself unknown, furnishes salts and esters that are important. It is the monoamide of carbonic acid and also may be regarded as aminoformic acid. The ammonium salt is formed when ammonium carbonate loses a molecule of water and, with ammonium bicarbonate that can be formed by loss of ammonia, makes up the official ammonium carbonate.



The esters can be prepared by the action of an alcohol on isocyanic acid or its polymer or by treating esters of chloroformic acid with ammonia.

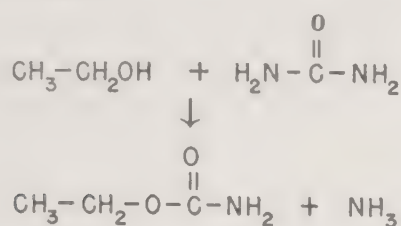


The ethyl ester is known as "urethane" and this has been adopted as a generic title for any of the esters. Alkyl and aryl derivatives have been made by starting with a corresponding isocyanate, and these compounds have also been called urethanes. The most common reagent for manufacturing them is phenyl isocyanate, and the phenylurethanes that are produced usually have characteristic melting points for identifying the alcohol.



Urethane (Ethyl Carbamate) U.S.P. occurs as colorless, odorless crystals or as a white, granular powder. It is very soluble

in water and in alcohol, and the aqueous solution is neutral to litmus paper. It is manufactured by heating urea and alcohol under pressure.



It can also be made by the action of the following: (1) urea nitrate on alcohol at 115–130° C., (2) ammonia on ethyl chloroformate, (3) carbamyl chloride on dehydrated alcohol, (4) potassium isocyanate on alcohol in the presence of hydrochloric acid, (5) ammonia on ethyl carbonate.

Urethane was formerly employed in medicine as a mild hypnotic and feeble diuretic in doses of 1 to 3 grams, but it almost has been abandoned for this purpose. It is now chiefly used as a solubilizing agent, as with quinine hydrochloride for sclerosing injections. It was once suggested as a good anesthetic (intraperitoneally) for laboratory animals, but detrimental side effects seem greater than they are with other agents. It recently has been used successfully in doses of from 3 to 5 grams daily for myeloid and lymphatic leukemia and in a maintenance dose of 2 grams daily to eliminate nodules of anaplastic undifferentiated cancer.

OFFICIAL OCCURRENCE

U.S.P.

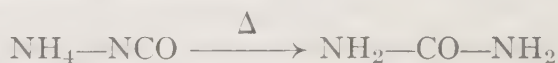
Quinine and Urethane Injection

Other simple urethanes have been proposed as hypnotics and sedatives, but none of these is now in much practical use. Among them could be mentioned: isoamyl carbamate (Aminoformate), methylpropylcarbinyl carbamate (Hedonal), tertiary amyl carbamate (Aponal), dichloroisopropyl carbamate (Aleudrin) and trichloroethyl carbamate (Voluntal). Chloral-urethane (Somnal, Ural), $\text{CCl}_3\text{—CHOH—NH—CO—O—CH}_2\text{—CH}_3$, and urethane-calcium bromide (Calmonal) have also been employed.

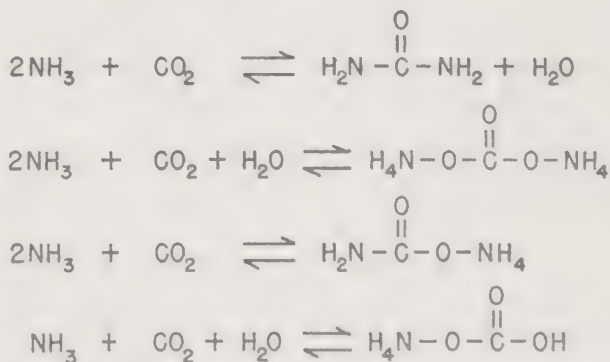
Dibutoline Sulfate, $[(\text{C}_4\text{H}_9)_2\text{N—COO—CH}_2\text{—CH}_2\text{—NH}(\text{CH}_3)_2\text{—CH}_2\text{—CH}_3]_2\text{—SO}_4$, is a carbamyl ester closely akin to the choline derivatives. Although not chemically related to atropine, it has almost the identical action locally without many systemic symptoms.⁷ It is used to produce mydriasis and cyclopegia by instilling one drop of a 5 per cent solution; the effects start in from 12 to 20 minutes, reach a maximum in from 40 to 60 minutes and last for 3 to 8 hours.

Urea (Carbamide) U.S.P., the diamide of carbonic acid, consists of colorless to white, prismatic crystals or a white powder. It is soluble in water (1:15) or in alcohol (1:10), and its aqueous solution is neutral to litmus.

Many methods for making this compound are known. They include the famous experiment by Wöhler in 1828, which proved that organic substances could be synthesized from the elements, that of heating ammonium isocyanate.

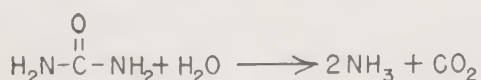
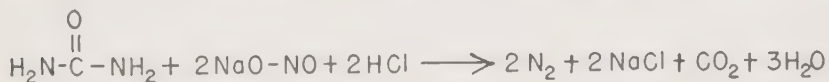
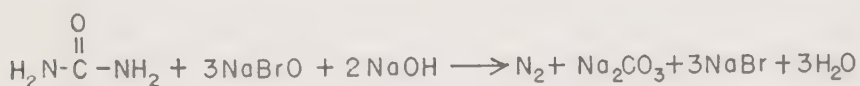


The most important process of preparation today is the combination of ammonia and carbon dioxide under the influence of carefully controlled heat and pressure. By changing these conditions only slightly, the same reagents can be made to produce ammonium carbonate, ammonium carbamate or ammonium bicarbonate. All of the reactions are highly reversible.



Urea is the normal excretion product for nitrogen in the urine of animals and con-

stitutes the chief solid in the urine of man, 5 to 60 grams per day. Its origin in metabolism, involving the amino acids arginine, ornithine and citrulline and the enzyme arginase, will be considered when the proteins are discussed. Determination of its amount in the urine may be performed in several ways, usually with sodium hypobromite, which produces nitrogen gas; with sodium nitrite and an acid, which gives about twice as much nitrogen, and with the enzyme urease to yield ammonia.



Urea is being used in industry in ever increasing amounts; the commercial grade (about 85 per cent) sells in quantity for less than 4 cents per pound (1948). Much of the tremendous quantity that is produced goes into the manufacture of fertilizer, and the rest is practically all consumed in making various plastics. Some is used in stabilizing explosives, for synthesizing compounds including medicinal agents, as a cattle food and for making varnishes, dyes, etc.

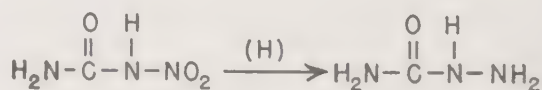
Urea also is of some importance in medicine, either administered internally or applied locally. It is practically nontoxic, even in large doses, and acts by osmosis like salines to give a fairly reliable diuresis. Of course, this is contraindicated in renal disease; indeed, the rate of excretion by the kidneys constitutes a useful means of testing (Van Slyke) for the efficiency of renal functioning. It is also employed locally to treat infected wounds; it has some antiseptic action and is said to promote granulation and healing, as well as to remove dead tissue. Strong solutions have been used to inject into the base of a wart in order to remove it.

Urea is said to promote the bacteriostatic activity of the sulfa drugs by inhibiting those substances that oppose them and by increasing the solubility and penetration. For such purpose it may be given by mouth or used topically. The oral dose is given officially as 8 grams, but amounts up to 30 grams have been employed several times daily. Fruit juices or other vehicles may be used to disguise the taste.

Afenil (Calcium Chloride Urea) N.N.R.

is a combination with the approximate formula $\text{CaCl}_2 \cdot 4(\text{NH}_2)_2\text{CO}$. It consists of colorless crystals that are soluble in water and not hygroscopic. It is marketed for intravenous injection of calcium chloride in the form of a 10 per cent solution, the dose of which is 10 cc.

Semicarbazide or aminourea is prepared by reducing nitrourea, produced when urea nitrate is exposed to sulfuric acid at low temperature.

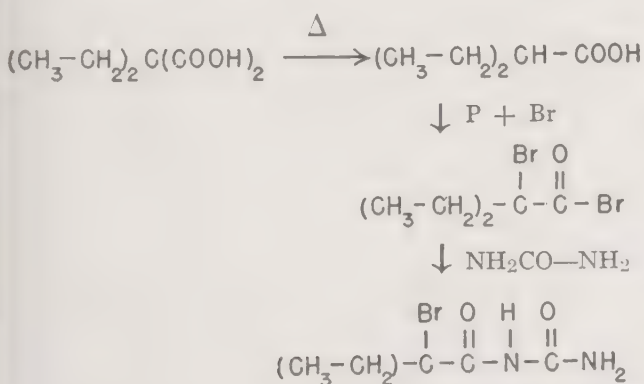


It is employed chiefly in the form of salts to make semicarbazones from aldehydes and ketones (q.v.).

Ureides. The acyl derivatives of urea are referred to as ureides and constitute a class of compounds that is very important in therapy. It includes the barbitals and many substitution products of pyrimidine and purine. Since either or both of the amino groups may be affected by the acylating agent and because polybasic acids may thus form cyclic compounds, the variety of ureides is almost unlimited. The following are a

few of those belonging to the aliphatic group: acetylurea, $\text{CH}_3\text{—CO—NH—CO—NH}_2$; diacetylurea, $\text{CH}_3\text{—CO—NH—CO—NH—CO—CH}_3$; carbamylurea or biuret, $\text{NH}_2\text{—CO—NH—CO—NH}_2$; carbonylurea or allophanic acid, $\text{NH}_2\text{—CO—NH—COOH}$; oxalylurea, $\text{NH}_2\text{—CO—NH—CO—COOH}$ and malonylurea, $\text{NH}_2\text{—CO—NH—CO—CH}_2\text{—COOH}$. It will be observed that in all ureides at least one of the nitrogen atoms is flanked by two carbonyl groups, and it is to be expected that its hydrogen atom could be replaced by metals to form salts, even if other nitrogen atoms in the molecule might be basic enough to form stable combinations with acids.

Carbromal (Bromodiethylacetylurea) N.F. (Adalin) occurs as a white, odorless, crystalline powder that is almost insoluble in water, but soluble in alcohol and in alkali hydroxides. It is prepared from diethylmalonic acid by heating to decarboxylate, treating with phosphorus and bromine and finally combining with urea.

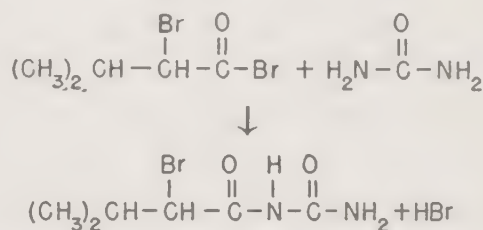


Carbromal is useful as a sedative and as a hypnotic in the milder forms of insomnia, although it is inferior to the barbitals in effectiveness. The chief applications are in neurasthenia, cardiac neuroses with tachycardia, chorea, mild mental disorders, whooping cough, mild epilepsy and other conditions of hyperirritability and insomnia due to internal diseases. The sleep that is produced is said to be restful and free from unpleasant after-effects. It is relatively

safe in doses of 0.3 to 1.5 grams repeated three or four times a day if necessary. The official dose is 0.5 gram.

Acetylcarbromal (Abasin) is a white powder that is slightly more soluble in water and is recommended in the same conditions as carbromal. It is used in doses of 0.25 to 0.5 gram.

Bromural N.N.R., 2-bromoisovalerylurea, is obtained by the action of bromoisovaleryl bromide on urea.



It is in the form of small needles that are slightly soluble in cold water but dissolve readily in hot water, in alcohol or in alkaline solutions. It is used in the same manner as is carbromal and in about the same doses, and it is said to be entirely detoxified or eliminated after from 3 to 4 hours. The corresponding iodine compound (Iodival) has been employed in 0.3 gram doses as an organic substitute for iodides.

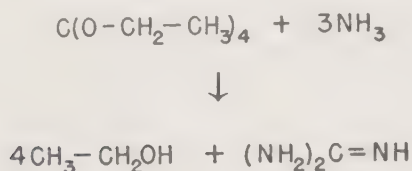
Another substance that is similar to carbromal is allylisopropylacetylurea (Sedormid), which has been recommended in doses of 0.25 to 0.5 gram. It will have been noted that these sedative ureides contain branched chains; those with normal chains have been found to be much less active.

Guanidine is derived from urea by substituting an imino group for the oxygen. It is a member of the class known as amidines,

characterized by the group $\text{—}\overset{\text{NH}_2}{\underset{\text{NH}}{\text{C}}}$, but

is much different from others of the class because this group is attached to amino, and the compound thus has a resonating structure. For this reason it is as strongly basic as the alkaline hydroxides. It is a colorless, hygroscopic solid that is soluble in water

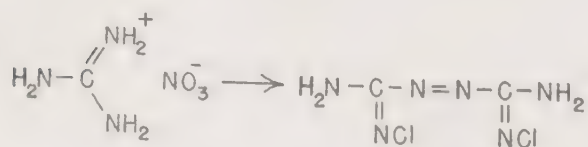
or in alcohol. It may be made from various derivatives of carbonic acid by a number of methods, including that from ethyl ortho-carbonate by the action of ammonia.



Guanidine is sometimes a useful substance for synthesizing compounds such as creatine, creatinine and other amino acids. When introduced into the body, it, as well as some of its derivatives, causes a lowering of blood sugar. Diguanidyldecane (Synthalin) was introduced into medicine for this action, but later it was found that the result is due to stimulation of the pancreas to produce more insulin and that, therefore, it is of no value in diabetes.

Guanidine Hydrochloride consists of colorless crystals that are very soluble in water or alcohol. It has been administered orally in the treatment of myasthenia gravis, the initial dose being 10 milligrams per kilogram of body weight, later increased to as much as three times that amount. In some cases, it may be given intravenously in a 2 per cent solution made isotonic with sodium chloride. The mechanism of action is obscure but possibly involves an increase in sensitivity of the skeletal muscle to acetylcholine.

Chloroazodin U.S.P. (Azochloramid, N,N'-Dichlorodicarbonamidine) "contains the equivalent of not less than 37.5 per cent and not more than 39.5 per cent of active chlorine (Cl)." It is prepared by treating a solution of guanidine nitrate in dilute acetic acid and sodium acetate with a solution of sodium hypochlorite at 0° C.

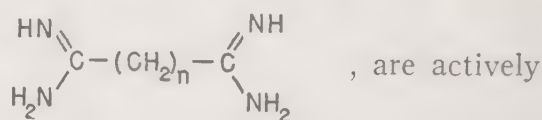


It consists of bright yellow needles or flakes with a faint odor of chlorine and a slightly burning taste, and it is explosive at about 155° C. It is not very soluble in water or other solvents, including glyceryl triacetate which is used to make the official solution, and the solutions decompose on warming or exposure to light.

Chloroazodin is similar to the chloramines and to sodium hypochlorite, but it does not react rapidly with water or reagents, and its action in use is relatively prolonged. Solutions are used on wounds (1:3,300), as a packing for cavities and for lavage and irrigation; dilutions up to 1:13,200 have been proposed for mucous membranes. For dressing and packing, the official, stable solution in glyceryl triacetate is employed, and a dilution of this in a vegetable oil (1:2,000) is claimed to be nonirritating to mucous membranes. Tablets of a saline mixture with buffer are available for making solutions.

OFFICIAL OCCURRENCE U.S.P.	PER CENT CHLOROAZODIN
Chloroazodin Solution	0.24-0.28

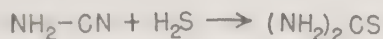
Diamidines, having the characteristic group on each end of a long chain,



trypanocidal; the maximum effect seems to be reached with undecane, or where n is 11. Later research⁸ showed that compounds with aromatic nuclei between the amidine groups were most efficient, so that the aliphatic compounds are not now used for this purpose.

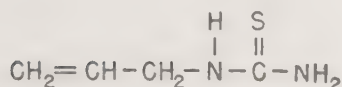
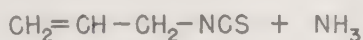
Thiourea N.N.R. is a white, crystalline solid that is soluble in water (1:11) but only slightly soluble in alcohol and the usual organic solvents. It may be prepared by heating ammonium thiocyanate, a method that is analogous to Wöhler's experiment in making urea from ammonium isocyanate, but this reaction is never complete. It is made

best by the reaction of hydrogen sulfide on cyanamide.



Thiourea was one of the first compounds known to have antithyroid activity, but it was soon superseded by thiouracil (q.v.) and its derivatives. It is at present employed only as an antioxidant for solutions of medicinal agents, such as metycaine; in aqueous solution it is easily oxidized to urea.

Thiosinamine (Allylthiourea, Rhodallin) consists of colorless crystals with a bitter taste and a faint odor. It is soluble in water (1:30) and is very soluble in alcohol and in ether. It can be prepared by the action of ammonia on allyl isothiocyanate.

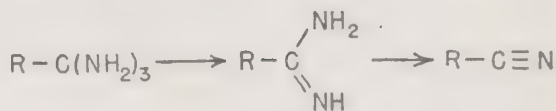


Thiosinamine was introduced into medicine⁹ in 1892 for the treatment of various conditions that are accompanied by the formation of fibrous tissue. These include burns, stricture of the esophagus or the urethra, keloids, sclerotic conditions of the ear and the central nervous system and arterial fibrosis. It also has been suggested as an agent against the dermatitis after injections of arsphenamine. In all cases, the method is not without danger and apparently requires more study. It is given orally in doses of 0.03 to 0.06 gram several times a day. A 15 per cent solution with sodium salicylate is marketed as Fibrolysin and is designed for intravenous injection; the contents of one ampule (2.3 cc.) is administered daily or every other day.

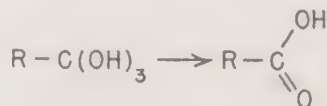
CYANIDES

The cyanides, R-CN , may be regarded as triamino hydrocarbons which have lost

ammonia, with the intermediate formation of amidines.



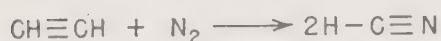
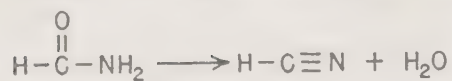
This is analogous to the loss of water from primary trihydroxy compounds to form meta acids.



They also may be regarded as esters of hydrogen cyanide, H-CN .

They are named alkyl cyanides just as the corresponding esters of the hydrogen halides are called alkyl halides but, because they all hydrolyze to acids and are chiefly used for this purpose, they are generally named as nitriles of these acids. The terms are coined by adding "onitrile" to the root of the acid. Thus, $\text{CH}_3\text{-CN}$ is methyl cyanide or acetonitrile and $\text{CH}_3\text{-CH}_2\text{-CN}$ is ethyl cyanide or propionitrile. In more complicated compounds, the prefix "cyano" may be used to designate the -CN group; this system would give cyanomethane and cyanoethane for the illustrations noted.

Hydrocyanic Acid (Prussic Acid), H-CN , is a colorless liquid boiling at about 26°C . and having a characteristic odor, usually said to be like that of peach blossoms. It occurs very widely in the vegetable kingdom, seldom in the free state but most often combined in glycosides (q.v.); the seeds of many species of *Rosaceae* contain such combinations. It may be prepared most conveniently by the action of mineral acids on its metallic salts, but it also is formed in many different ways. As examples, there might be mentioned: heating of chloroform with ammonia under pressure, dehydration of formamide or formaldoxime and the action of an electric spark on a mixture of acetylene and nitrogen.



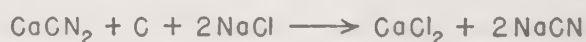
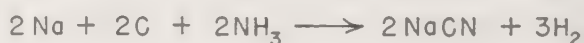
Hydrogen cyanide is a very weak acid, so much so that carbonic acid will liberate it from the alkali salts; the dissociation constant is about 1.3×10^{-10} . It is very unstable, even in dilute aqueous solution, but may be preserved by traces of mineral acids. Warming of such a solution, however, brings about complete hydration to ammonium formate, $\text{H}-\text{CO}-\text{O}-\text{NH}_4$. Because of its unsaturated character, it easily adds other substances besides water, e.g., aldehydes and ketones to give cyanohydrins, nascent hydrogen to yield methylamine and the Grignard reagent to give compounds that hydrolyze to aldehydes. In many of its reactions, as well as those of the metallic salts, hydrogen cyanide behaves as if it were a mixture of two tautomeric compounds, $\text{H}-\text{CN}$ and $\text{H}-\text{NC}$; the latter is called hydrogen isocyanide.

Hydrogen cyanide and its soluble salts are among the most rapid of all poisons although the minimum fatal dose is not especially low. If the dose has been large, as is usually the case, the victim falls within a few seconds and dies very shortly afterwards, without any symptoms other than one or two convulsions. With smaller but fatal amounts, the symptoms are headache, confusion, muscular weakness, difficulty in breathing, dilated pupils, unconsciousness, violent convulsions, involuntary evacuations and failure of respiration. The effects ensue so rapidly that death is seldom delayed more than 30 minutes, and recovery is the rule if death does not occur within one hour. Any good oxidizing agent will destroy cyanides before they have been absorbed, but an efficient antidote for the systemic action is difficult to find because this action is so

rapid. Among those that have been proposed are methylene blue, sodium tetrathionate, sodium nitrite and sodium thiosulfate. A combination of sodium nitrite intraperitoneally and sodium thiosulfate intravenously seems to have given the best results in cattle.

A diluted solution (about 2 per cent) formerly was used as an addition to cough remedies, but is seldom prescribed today except occasionally in animals. The official syrup of wild cherry contains some hydrogen cyanide but is chiefly used as a vehicle for more useful remedies.

The metallic cyanides are very important in industry and in analytical chemistry and are probably already quite familiar to the student. The alkali salts formerly were prepared by heating potash or soda with iron and animal or vegetable refuse, but the more modern methods are to heat the metal with carbon and ammonia and to heat calcium cyanamide with carbon and a chloride.

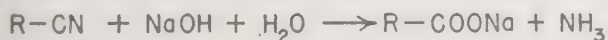
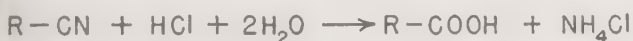


Other salts, which are mostly insoluble, can be made by precipitation or by the action of hydrogen cyanide on the oxides or hydroxides. In producing them by precipitation, any excess of reagent tends to dissolve the product by forming a soluble complex. Among important compounds of this class are: potassium ferrocyanide or yellow prussiate, $\text{K}_4\text{Fe}(\text{CN})_6 \cdot 3\text{H}_2\text{O}$; potassium ferricyanide or red prussiate, $\text{K}_3\text{Fe}(\text{CN})_6$; sodium nitroprusside or nitroferricyanide, $\text{Na}_2\text{Fe}(\text{CN})_5\text{NO} \cdot 2\text{H}_2\text{O}$, and Prussian blue or ferric ferrocyanide, $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$. Mercuric cyanide and mercuric oxycyanide will be described in a later chapter.

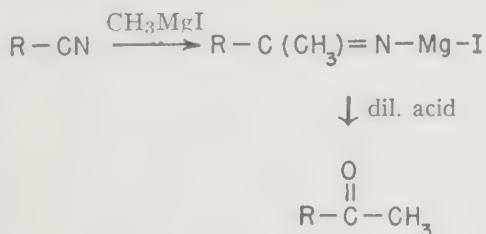
The alkyl cyanides or nitriles are chiefly of importance because they furnish a convenient means for preparing acids. They are usually made by heating halides with alkali cyanides in alcoholic solution; the small

amount of isocyanide that is formed may be removed by shaking with hydrochloric acid. Halides of tertiary alcohols are not satisfactory because they furnish mostly olefines. The nitriles also can be prepared by the dry distillation of ammonium salts with dehydrating agents, by the Hofmann degradation of higher amides, by the dehydration of amides or oximes and by the distillation of acids with metallic thiocyanates.

They are colorless, aromatic liquids that distill without decomposition; they are insoluble in water and nonpoisonous. As has been noted, their most useful reaction is the ability to hydrate to ammonium salts through an intermediate amide and thus to form acids. While this can be brought about gradually by boiling with water, it is most conveniently performed by boiling with acid or alkali.

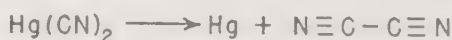


Reduction of nitriles yields primary amines; this is most easily accomplished by sodium and absolute alcohol. They will add, among other substances, the Grignard reagent to produce a ketone; hydrogen cyanide yields an aldehyde under the same conditions.



Cyanamide, NH_2-CN , the nitrile of carbamic acid, is formed in a large number of reactions, including the dehydration of urea by thionyl chloride, but is most conveniently prepared from its salts by the action of mineral acids. Because of its great reactivity, it is very useful in synthesis; for example, guanidine derivatives are produced by the action of amines. Calcium cyanamide,

$CaNCN$, is prepared in large quantity commercially by passing nitrogen (from the air) over heated calcium carbide. It is largely used as a fertilizer or to prepare other nitrogenous compounds. Other derivatives of hydrogen cyanide that are useful in synthesis are dicyanogen, a poisonous gas made by heating mercuric cyanide, and cyanogen halides, which can be prepared by the action of halogen on hydrogen cyanide.



Isocyanides or **carbylamines**, $R-NC$, are made by heating alkyl halides with silver cyanide. In this process, some nitriles are also produced, while if alkali cyanides are used in place of the silver salt, the chief products are nitriles. They also can be prepared by distilling a mixture of chloroform, a primary amine and a base.



This reaction demonstrates that the alkyl radical is connected to nitrogen and it also serves to identify the presence of a primary amine, because the isocyanides are poisonous liquids with an extremely disagreeable and characteristic odor. The formulas are usually written with no bonds between nitrogen and carbon but, in the light of modern ideas as to structure, they are perhaps best represented as $R-N \equiv C$ or $R-N^+ \equiv C^-$ to show the difference in charge within the molecule. In any event, they are very reactive compounds and are sometimes of great value in synthesis.

Isocyanates. Metallic cyanates can be made by oxidizing cyanides with air, oxides of lead, potassium permanganate or other agent. When acidified at low temperature, they form cyanic acid ($HO-CN$), a volatile liquid that is only stable below $0^\circ C$. At higher temperatures it polymerizes to cyan-

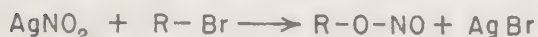
uric acid, a heterocyclic compound. When a metallic cyanate (MNCN) is distilled with an alkyl halide or sulfate or when a carbylamine is oxidized with mercuric oxide, esters of isocyanic acid are produced; those of cyanic acid, $\text{H}-\text{O}-\text{CN}$, are not known.



These esters are volatile liquids with a disagreeable, pungent odor and are quickly polymerized if the radical is small. They react readily with alkalis to yield primary amines, with ammonia to form alkylated ureas and with alcohols to form urethanes. The last reaction, using aryl isocyanates such as the phenyl compound, is often employed for identifying the alcohol.

NITRO AND NITROSO COMPOUNDS

Nitro compounds, $\text{R}-\text{NO}_2$, of the aliphatic series may be prepared by heating silver nitrite with a halide, but an isomeric nitrite is produced at the same time.



They also can be made by direct action of nitric acid (nitration) on paraffin hydrocarbons, especially when the attack can be made on hydrogen attached to tertiary carbon, although the reaction is slow and the yields are poor.



Recently it has been found that the nitro compounds can be prepared commercially from the lower paraffins by vapor phase reaction (about 400°C .), although a mixture is always obtained because of some pyrolysis.

The aliphatic nitro compounds, particularly those in which the group is connected to a primary or secondary carbon, are very

reactive and promise to be quite useful in synthetic procedures. For example, the primary derivatives react with aldehydes or ketones to produce nitroalcohols and nitroolefins; also, boiling hydrochloric acid converts them to fatty acids, for example, propionic acid from 1-nitropropane. In addition, of course, they can all be reduced to primary amines as can tertiary compounds of the aromatic series. The latter at present are far more important; the details of reactions and structure will be discussed in connection with these.

Chloropicrin (Nitrochloroform), CCl_3-NO_2 , a colorless liquid with an intense, penetrating odor, was used in World War I because its vapors cause much lacrimation and a frontal headache. It is made by the action of chlorinated lime on picric acid. In recent years it has been used in industry as insecticide and vermicide.

Nitroso compounds, characterized by the group $-\text{NO}$, are of considerably less importance. The nitrosamines in which the group is connected to nitrogen have already been mentioned. Those in which the group is attached to a tertiary carbon are blue in color but rapidly pass into polymeric, colorless modifications, an action which is reversed by heat or solution. In general, the primary and secondary derivatives cannot be isolated because they are immediately transformed to tautomeric oximes.



The preparation of a nitroso compound is carried out by means of nitrous acid, using a metallic nitrite and a mineral acid, or best perhaps by nitrosyl chloride with the aid of sunlight. Like the nitro compounds, the nitroso derivatives easily can be reduced to primary amines.

Numerous other classes of nitrogenous compounds are known and are sometimes of importance in laboratory procedures, but the details of these are beyond the scope of this volume. Among them might be mentioned

derivatives of hydrazine, $R-NH-NH_2$, and hydroxylamine, $R-NHOH$, and the diazoparaffins, of which diazomethane, CH_2N_2 , has received most study.

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11

Aromatic Hydrocarbons

The aromatic hydrocarbons are of little importance as medicinal agents. Of course, in many cases they are the nuclei for more active and desirable compounds, but as yet no medicinal application has been found for the aromatic hydrocarbons. Carcinogenic properties have been observed and studied for some of the more complex aromatic hydrocarbons.

Aromatic character and aromaticity are terms that are used in reference to cyclic compounds such as benzene, naphthalene, phenanthrene and anthracene. Also, aromatic character is found in some heterocycles. Historically, the term may have been introduced in connection with odor or aroma of some organic compounds. To define the term "aromatic character" clearly and quickly is most difficult since such a characteristic is associated with several chemical phenomena. When the chemical properties of benzene are compared to those of the unsaturated alkenes and alkynes, the diminished unsaturation reactivity and the tendency to the formation and preservation of structural type are impressive. That benzene is unsaturated has been unquestionably established, yet it is so much less reactive than hexatriene ($\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$) that the unsaturation seems to be of a modified special character. In contrast to the simple alkenes and alkynes, benzene reacts

only slowly with bromine and is inert toward hydrogen bromide. It decolorizes weak, cold, acidic solutions of potassium permanganate but does not decolorize alkaline permanganate solutions, whereas olefins quickly decolorize acidic or basic permanganate. The stability of the unsaturated ring system of benzene and its ease of formation is exhibited by the fact that aromatic type compounds are produced by the pyrolysis of coal, the dehydration of camphor with phosphorous pentoxide to *p*-cymene and dehydrogenation reactions with sulfur, selenium and palladium.

A specific character of these aromatic compounds is that most of their reactions are substitutions; this is in contrast to the reactions of alkenes and alkynes, which are additions. Picric acid, under suitable conditions, reacts to form complexes that are called picrates¹ with the condensed ring polynuclear hydrocarbons. These complexes, due to specific melting points, are useful as derivatives for identification and, since the hydrocarbon can be regenerated, are important for their purification.

Benzene (Benzol). The chief source of benzene (C_6H_6) is coal tar, from which it is obtained in yields of 1 to 2 per cent. Sometimes impurities such as toluene, carbon disulfide and thiophene may be present.*

* Note U.S.P. XIII, Thiophene Test, p. 747.

Although impractical and rarely done, benzene may be obtained by the following methods: (1) heating phenol with zinc, (2) distilling sodium benzoate and soda lime and (3) passing acetylene through a tube heated to 500° C.

It is a water-white liquid having a burning taste and an aromatic odor. Benzene is miscible with alcohol, chloroform, ether, acetone, glacial acetic acid or oils and is immiscible with water. It is thus a good solvent for fats, resins or certain alkaloids. The vapor of benzene is highly inflammable, producing much soot, and forms an explosive mixture with air in concentrations of 1.5 to 8.0 per cent.

The toxic properties of benzene² have been known for many years. Reports indicate that 0.037 Gm. produces a toxic effect in mice. Inhalation of benzene vapor in air causes acute or chronic poisoning, depending upon the concentration of the vapor and the length of the exposure.³ Inhalation of high concentration of vapor (above 3,000 parts per million by volume in air) even for short periods of time (a few minutes) results in acute poisoning. The onset of symptoms is characterized by tightening of the leg muscles, dizziness, excitement, breathlessness and a sensation of pressure on the lower central part of the forehead. The secondary reactions are those of confusion and hysterical expressions such as cursing, laughing and singing. In most cases the victim becomes very obstinate.

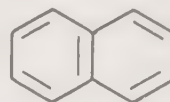
External contact with benzene should be avoided because of the defatting effect and irritant action. Repeated exposure may establish serious, abnormal skin conditions.

Chronic poisoning may develop from daily exposures to air containing more than 100 parts per million by volume of benzene vapor over a period of weeks or months. An early symptom of chronic poisoning is anemia, due to the effect of benzene on the blood-forming function of the bone marrow. Thus, a decrease in the number of blood

platelets, and white and red blood corpuscles is observed; this greatly lowers the resistance to infection. Tetrachloroethane is the only commercial solvent that is more dangerous than benzene.

Benzene has been used in medicine to meet a variety of situations; some of its uses are as an antispasmodic, antiseptic, parasiticide and for trichinosis and leukemia. It is not only dangerous to use (q.v.), but also is of doubtful value. In a few conditions, such as myeloid chloroleukemia, benzene has been shown to be helpful.⁵ Benzene and related compounds, such as toluene and xylene, are useful as preservatives, antiseptics and parasiticides. Toluene is a good preservative for urine samples intended for either chemical or microscopic examination. Benzene type compounds increase in activity by the substitution of an alkyl group in the ring. The activity increases with the length of the alkyl group, but if two or more alkyl groups are introduced the activity decreases (i.e., toluene > *p*-xylene > *m*-xylene > *o*-xylene).

Naphthalene (Tar Camphor). The structure for naphthalene (C₁₀H₈) was postulated in 1886 and since has been accepted.



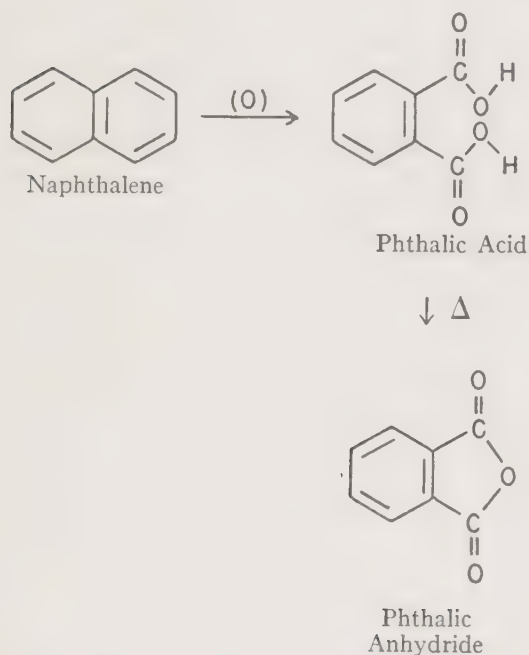
Naphthalene

The chemical knowledge concerning the structure is enormous and is a subject of research study even today. Coal tar yields about 11 per cent of naphthalene and is the principal source. Synthetic methods of preparation are known; some of these are pyrolysis of benzene, heating 1,2-dibromoethylbenzene with zinc dust or reducing and then dehydrogenating α -tetralone. None of these methods have any commercial value.

Naphthalene occurs as glistening white crystalline plates, having a sharp taste and a characteristic odor. The crystals are soluble in organic solvents (hot alcohol, but diffi-

cultly soluble in cold alcohol) and insoluble in water. The solid readily sublimes and will vaporize slowly under normal conditions (an exposed moth ball vaporizes in about three months).

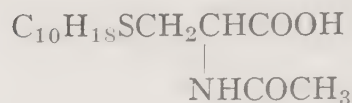
Naphthalene is composed of two six-membered rings, one truly aromatic in character (as benzene) and the other, more aliphatic in character. Because of this, it enters into both substitution and addition reactions. It can be regarded as a benzene derivative having unsaturated carbon chains ortho to each other with their ends fused to form a ring. This ring is opened easily by oxidation, thus providing the main source of phthalic acid and phthalic anhydride.



These are important in the preparation of anthranilic acid and dye intermediates. Tetralin and decalin are produced readily by the reduction of naphthalene.

Naphthalene is widely used as a starting material for a host of related compounds. It has some use as a moth repellent and insecticide, but this use is becoming less important since the introduction of newer compounds, such as *p*-dichlorobenzene.

When, by chance, it becomes ingested it may be detoxified as a derivative of mercapturic acid.



Anthracene, ($\text{C}_{14}\text{H}_{10}$). This hydrocarbon is recovered from anthracene oil, b.p. $270\text{--}360^\circ \text{C.}$, obtained by the distillation of coal tar. The carbon atoms are so arranged as to form a tricyclic structure of three unsaturated six-membered rings attached ortho to each other and lying in the same plane. It is present in the oil from 20 to 30 per cent and about 1 per cent in coal tar.

Anthracene occurs as colorless crystalline plates that have a blue fluorescence.

The crystals dissolve in most organic solvents, are less soluble in alcohol or ether and are insoluble in water.

It is readily oxidized to anthraquinone and is reduced to any one of its hydro-compounds. Anthracene, as would be expected, forms many substitution derivatives and, as such, is important as an intermediate in the manufacture of anthraquinone, alizarin and alizarin dyes.

Phenanthrene ($\text{C}_{14}\text{H}_{10}$) is a structural isomer of anthracene isolated in the same oil fraction from the distillation of coal tar. The hydrocarbon occurs as white glistening plates, soluble in ether, benzene, alcohol, glacial acetic acid or carbon disulfide, but insoluble in water. Solutions of it possess a blue fluorescence.

Phenanthrene at present is used only for a few dye stuffs. Phenanthrene, partially or completely reduced, is closely related chemically to certain alkaloids such as morphine and codeine, to certain terpenes such as retene and abietic acid, and is an essential portion of sterols, bile acids and some sex hormones. The phenanthrene nucleus is also present in some of the sapogenins of the digitalis saponins. Likewise, it is present in

the aglucons of the cardiac glycones and the genins of the toad poisons.

In 1908⁶ a study was made to determine the physiologic effects of hydrogenated phenanthrene derivatives. This investigation showed that toxicity decreased in a logarithmic order with the increase of hydrogenation.

Carcinogenic Hydrocarbons. Since the work of I. W. Cook,⁷ there have been many studies^{8, 9} concerning aromatic hydrocarbons and their cancer-producing properties. Some of the compounds thought to possess carcinogenic properties are pyrene, chrysene, 1,2,5,6-dibenzanthracene,¹⁰ 1,2-benzanthracene and methylcholanthrene.

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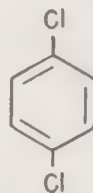
Aromatic Halogenated Compounds

The halogenated aromatic hydrocarbons have not been found useful as medicaments, although many are used. They are quite toxic and vary in physiologic response according to which one of the halogens is present and whether the halogen is attached to the aromatic ring or is in a side chain. Substituting a halogen for a hydrogen on the nucleus of an aromatic hydrocarbon (chlorobenzene) increases the toxicity and does not impart any sedative or anesthetic effect. The order of toxicity is approximately the following: toluene < *o*-chlorotoluene < *m*-chlorotoluene < *p*-chlorotoluene. Increasing the number of halogen atoms in the hydrocarbon lessens the toxicity. This is explained by the decrease in solubility of the halogenated hydrocarbons. Thus, the order of toxicity is: chlorobenzene > 1,4-dichlorobenzene > 1,3,5-trichlorobenzene. Where water solubility is not a limiting factor, an increase in the number of halogens contained in the aromatic compound will give rise to increased toxicity.

The halogenated aromatic hydrocarbons, such as benzyl bromide and chloromethyltetralin, that have the halogen in a side chain have decided lacrimatory properties. Exposed skin is also attacked, with resulting redness and discomfort.

Dichloricide (*p*-Dichlorobenzene). Benzene, upon being treated with chlorine, produces a mixture of from two to six chlorina-

tion products. If the temperature is regulated and a suitable catalyst is used, the degree of chlorination can be controlled. Benzene treated with chlorine below 400° C. and in the presence of aluminum chloride produces a mixture of *o*-dichlorobenzene (30 per cent) and *p*-dichlorobenzene. Since the ortho form is a liquid (m.p. —17.6° C.) and the para form a solid, under normal conditions they are readily separated.



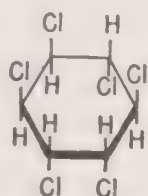
Dichloricide

Dichloricide occurs as white crystals having a characteristic odor. The crystals are soluble in organic solvents and insoluble in water. It has been suggested for many uses, such as an antiseptic, an itch remedy and as a germicide. The most important uses appear to be in the protection of fabric and furs against moths and other insects and in the control of the peach tree borer.¹

Benzene Hexachloride* (1,2,3,4,5,6-Hex-

* Benzene hexachloride is actually an alicyclic compound and not an aromatic. It is included here because of its name and because it is prepared from benzene.

achlorocyclohexane, 666, Gamex, Gamnexane). This halogenated compound was first prepared in 1825 and has been a subject of research since that time. Bender,² in 1935, reported the value of benzene hexachloride as an insecticide in his patent dealing with its preparation by the addition of benzene to liquid chlorine.



Benzene Hexachloride

Benzene hexachloride is a mixture of a number of isomers, five of which have been isolated. The gamma isomer, which is present to the extent of 10 to 13 per cent in the commercial product, is by far the most active form and is responsible for the insecticidal property. The formula given here corresponds to one of the optically active inositols which would, of course, have OH groups substituted for the chlorine. Whether or not this formula corresponds to the gamma isomer is not known.

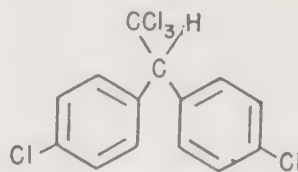
In powder form it has a light buff to tan color, a persistent musty odor and a bitter taste. It is insoluble in water but readily soluble in many organic solvents³ such as xylene, carbon tetrachloride, methanol, benzene or kerosene. The compound is unusually stable in neutral or acid environments. It withstands the effect of hot water and may be recrystallized from hot concentrated nitric acid. In the presence of alkalis such as dry lime or lime water, however, hydrogen chloride is readily split out, leaving a mixture of the isomers of trichlorobenzene.

Benzene hexachloride exhibits three modes of action against insects: (1) contact, (2) fumigant and (3) stomach poison. Insects which are susceptible to it are affected most by the first two modes of action since the effect is rapid and the contact or fumigant action is felt before enough material can be eaten to be lethal. Physiologically,

the effect upon insects seems to be the same as with DDT, that is, the nervous system is affected first. The most promising application is in the destruction of cotton insects, aphids of fruits and vegetables and in the treatment of scabies in animals and man.

Toxicity of this compound to warm-blooded animals is about the same as, or lower than, DDT and, although it may be irritating to some people, recent studies indicate that a considerable quantity would have to be ingested before any ill effects are produced.

DDT [2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane]. Zeidler,⁴ who first prepared the insecticide, DDT, obtained the compound by the reaction between chloral and chlorobenzene in the presence of sulfuric acid. Practically all of the processes used to prepare DDT are modifications⁵ of the original method of Zeidler. In 1939,⁶ its insecticidal properties were discovered.



DDT

DDT is a white, waxy solid with a very faint, fruity odor. Sometimes it is marketed as a cream or gray powder. It is practically insoluble in water, but is soluble in organic solvents. It is stable in aqueous alkali, but in alcoholic alkali it loses hydrogen chloride, and, consequently, its effectiveness.

Study of the action of DDT on certain insects indicates that it is both a contact and a stomach poison. The contact action appears to depend upon its effect on the nervous system of insects. It is distinctly toxic to warm-blooded animals when ingested or if absorbed through the skin.⁷

DDT as an insecticide has a wide range of effectiveness, particularly for lice (typhus), mosquitos (malaria), house flies and moths.

Chlordane (1,2,4,5,6,7,8,8-octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane, 1068, Octa-Klor, Synklor). This chlorinated hydrocarbon was first reported in 1945.⁸ It exhibits a high order of toxicity to a wide range of insects and related arthropods. Lethal action on susceptible organisms may result from direct contact, from ingestion or from exposure to its vapor. This product is mild in action to warm-blooded animals, and therefore, may be used safely for insect control under a wide variety of circumstances.

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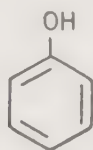
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Phenols and Their Derivatives

PHENOLS

PHENOLS

A phenol is a compound in which a hydrogen atom of an aromatic nucleus has been replaced by a hydroxyl group (OH). As



Phenol

such it becomes structurally a special tertiary alcohol. Because aromatic nuclei have a number of similar replaceable hydrogens, more than one such hydroxy substitutions are possible. For example, benzene has six such similar replaceable hydrogens, and, thus, the maximum number of hydroxyl groups that can be introduced in benzene would be six. When monohydroxy substitution in benzene alone is considered, only one product, by virtue of all positions being similar, is possible, viz., hydroxybenzene or phenol itself. It becomes obvious that one or more of the hydrogens of the aromatic nuclei also can be replaced by one or more of a number of groups such as:

Alkyl Thymol
Substituted alkyls Neosyneprine, Stilbestrol
Carboxyl Salicylic Acid

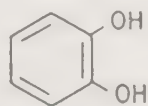
SYNTHETIC ESTROGENS

TANNINS

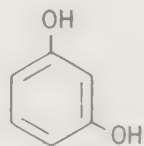
Aldehyde Salicylaldehyde
Halogens Tribromophenol
Nitro Picric Acid
Sulfonic acid Phenolsulfonic Acid

It follows that a large number of variously substituted monohydroxybenzenes or phenols are possible. A number of these compounds have been found in nature (e.g., thymol and carvacrol) or have been prepared synthetically (e.g., chlorothymol, chlorohexol and trinitrophenol) and are used as drugs in medicine.

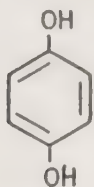
In the case of dihydroxy substitution in benzene, three isomers are possible for structural reasons, for example:



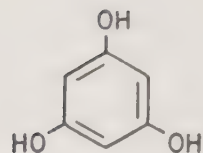
Catechol, 1,2-Benzenediol, *o*-Dihydroxybenzene, Pyrocatechol or 1,2-Dihydroxybenzene



Resorcinol, 1,3-Benzenediol, Resorcin, *m*-Dihydroxybenzene or 1,3-Dihydroxybenzene



Hydroquinone, 1,4-Benzenediol, 1,4-Dihydroxybenzene, *p*-Dihydroxybenzene or Quinol



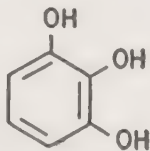
Phloroglucinol, 1,3,5-Benzenetriol, or 1,3,5-Trihydroxybenzene

The hydrogen attached to the benzene nucleus also may be replaced by the groups as described under phenol, with the production of a number of variously substituted dihydroxybenzenes, such as:

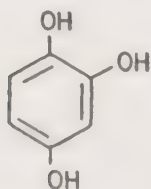
Alkyl	Eugenol and nordihydroguaiaretic acid
Substituted alkyl ..	Epinephrine and coniferyl alcohol
Carboxyl	Protocatechuic acid
Aldehyde	Vanillin
Alkyl	Hexylresorcinol

A number of these compounds have been found in nature (e.g., eugenol, guaiaretic acid, nordihydroguaiaretic acid and urshiol), have been prepared from natural products, (e.g., cresols from coal tar, guaiacol from wood tar and pyrogallol from gallic acid), or have been prepared synthetically (e.g., hexylresorcinol).

Only three trihydroxybenzenes are also possible for structural reasons. These are:

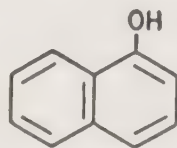


Pyrogallol, 1,2,3-Benzenetriol, 1,2,3-Trihydroxybenzene or Pyrogallic Acid

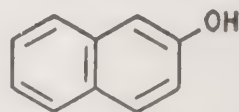


1,2,4-Benzenetriol, 1,2,4-Trihydroxybenzene or Unsymmetrical Trihydroxybenzene

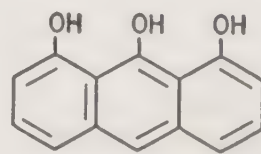
In the hydroxy substituted naphthalenes, the monohydroxy substituted compounds, namely, 1 and 2-naphthols or alpha and beta-naphthols are the most significant. 2-Methyl-1,4-naphthohydroquinone is a precursor to menadione and, on a mole for mole basis, is as physiologically active as menadione. (See vitamin K in the chapter on vitamins.) Although many other polyhydroxy naphthols and substituted naphthols are possible, few are encountered in medicine. This is also true of other polycyclic compounds (anthracene and phenanthrene), that contain one or more phenolic hydroxyl groups. 1,8,9-Trihydroxy phenanthrene is used in medicine.



α -Naphthol



β -Naphthol

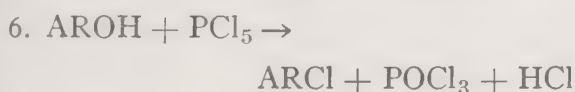
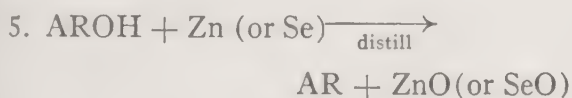
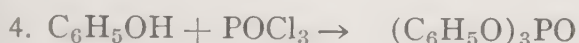
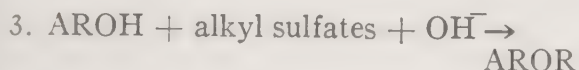
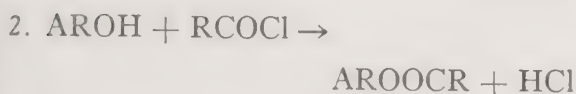
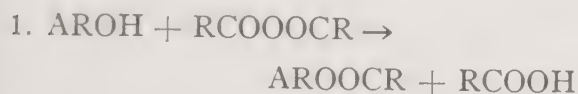


1,8,9-Trihydroxyanthracene

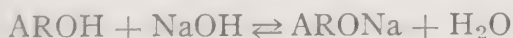
Anthrahydroquinone does not occur in nature. It is readily oxidized to anthraquinone. Substituted anthraquinones do occur in nature; they are phenolic compounds such as barbaloin, aloin and rhein. These compounds are discussed in Chapter 14. No phenanthrene compounds containing phenolic hydroxyl groups are used as medicinal agents. However, partially reduced and substituted phenanthrene structures containing phenolic hydroxyl groups are present in some of the most useful drugs, such as morphine, estradiol, etc.

PROPERTIES

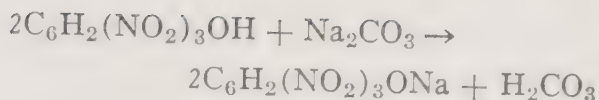
Because phenols are characterized by the OH group, they undergo many of the reactions characteristic of alcohols (see Chapter 6).



Although phenols can be considered, from one standpoint, as tertiary alcohols, they differ from alcohols in that they are weakly acidic. This acidity is a function of the structure of the hydroxyl groups attached directly to the unsaturated nucleus or to the presence of the enolic grouping $-\text{CH}=\text{C}(\text{OH})-$. The acidic properties of phenols are modified by electron attracting or repelling substituents. Thus, for example, phenol ($K_a = 1 \times 10^{-10}$) will form salts with sodium or potassium hydroxide but not with their corresponding carbonates. On the other hand, the introduction of electron attracting groups such as nitro groups increases the acidity of phenols, depending



on the number of nitro groups introduced. For example, the mononitrophenols have acid dissociation constants of $1-7 \times 10^{-8}$; 2,4-dinitrophenol, $K_a = 1 \times 10^{-4}$, and trinitrophenol or picric acid is nearly as strongly acidic as a mineral acid and will decompose carbonates.

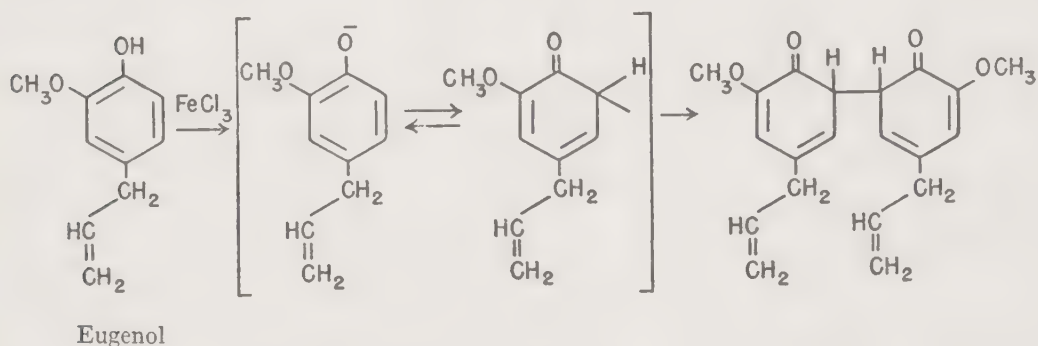
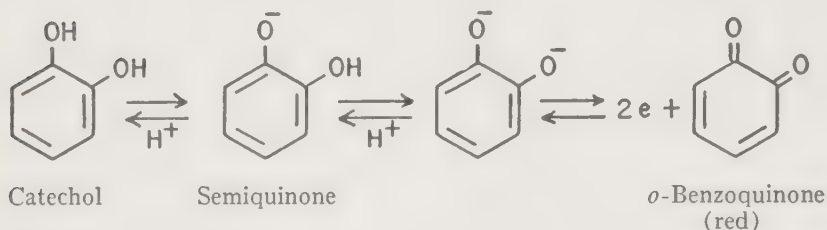
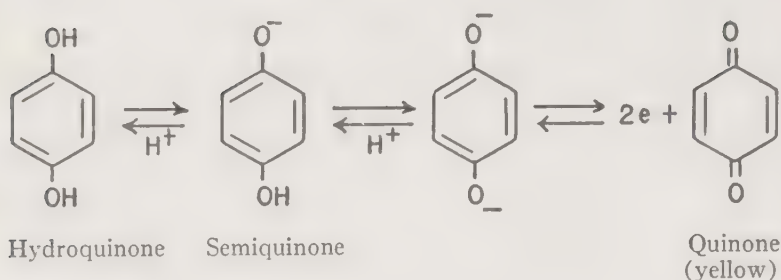


Although, as a general rule, with the increase in the number of hydroxyl groups an increased solubility in water is obtained, no such uniform rule follows with the polyhydroxyphenols, as is evidenced by the following solubility data.

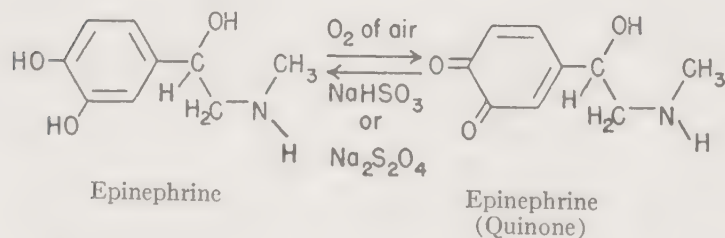
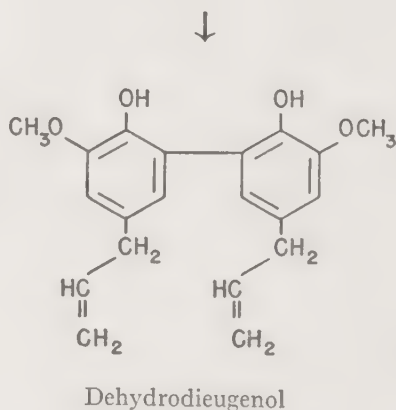
COMPOUND	SOLUBILITY (GM. IN 100 CC. H ₂ O)
Catechol	45 Gm.
Resorcinol	123 Gm.
Hydroquinone	8 Gm.
Pyrogallol	62 Gm.
Phloroglucinol	7.7 Gm.

Many phenols give characteristic colors with ferric chloride in very dilute aqueous or alcoholic solutions. Sometimes very strong alcoholic solutions are required to obtain a color test. These colors vary with the phenol and the number and position of the phenolic hydroxy groups. For example: phenol—violet, guaiacol—blue to green, cresols—blue, catechol—green, resorcinol—dark violet, pyrogallol—bluish black.

Phenols are susceptible to attack by oxygen of the air and by oxidizing agents such as ferric chloride, chromic acid, etc. The oxidation of the polyhydroxy phenols by air is very markedly accelerated by the presence of alkali. In the case of catechol, it takes place in a matter of minutes, and with pyrogallol, the reaction is quantitative. Those polyhydroxyphenols in which the hydroxyl groups are ortho or para to each other are particularly susceptible to oxidation. One form of oxidation as an initial step may consist of the removal of a hydroxylic hydrogen atom, with the formation of a free radical containing univalent oxygen. Such radicals (semiquinones in some cases) are usually so unstable and reactive that they are quickly converted to the quinone or to other secondary products such as quinhydrone, dimers and dehydrodiphenols:



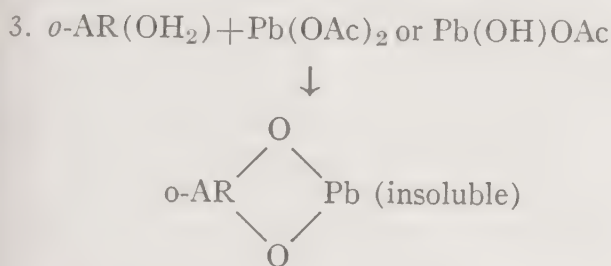
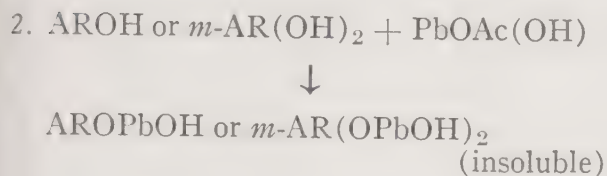
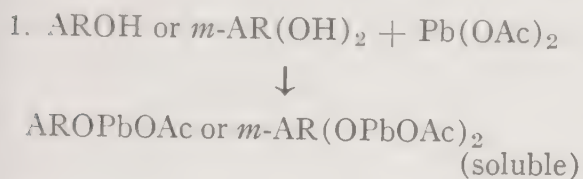
The sensitivity of phenols and compounds containing phenolic hydroxyl groups to oxidation is a problem with many drugs, and special storage conditions and preservatives such as bisulfites and hydrosulfites are used to prevent oxidation or prolong their usefulness. For example, catechol or drugs containing catechol groups (epinephrine) when marketed in solution, contain one of these preservatives to prevent the following change.



Monohydroxyphenols in general are not precipitable by lead acetate or the acetates of other heavy metals, i.e., barium; however, many are precipitated from solution by basic

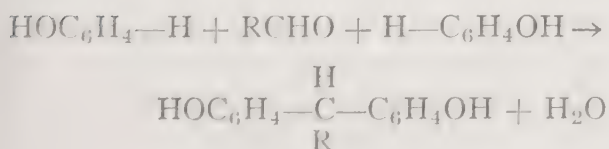
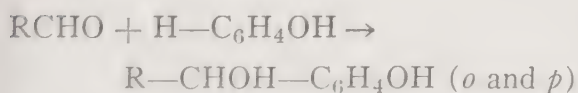
lead acetate. This is also true of polyhydroxy phenols in which the hydroxyl groups are not adjacent to each other. Polyhydroxyphenols in which the hydroxyl groups

are adjacent to each other are precipitable from aqueous and aqueous ethanol solutions by means of lead acetate or basic lead acetate, barium hydroxide, cupric acetate, etc.



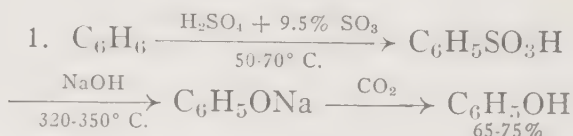
A number of polyhydroxyphenols, particularly those that have three adjacent hydroxyl groups, will combine with and precipitate or coagulate proteins. Although no direct evidence is available, catechol type phenols such as urushiol, the toxic principle of the poison ivy, appear to combine quite firmly with protein.

Phenols will condense readily with aliphatic and aromatic aldehydes with or without the aid of catalysts and/or heat. This property is particularly true of some of the polyhydric phenols, such as resorcinol which will combine with formaldehyde in the cold. The extent of polymerization depends upon the ratio of aldehyde to the phenol.

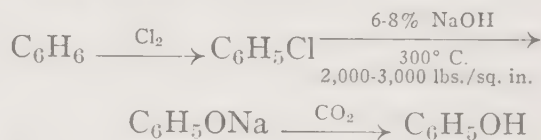


USE IN PHARMACY

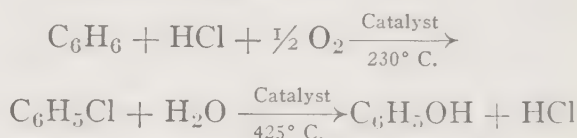
Phenol (Carbolic Acid) U.S.P. Phenol is monohydroxybenzene obtained from coal tar in 0.7 per cent yield by extraction with alkali. The phenolates are decomposed, and the phenolic fraction subjected to fractional distillation for the separation and purification of the individual phenolic fractions. This source of phenol was not sufficient to meet the demand, and phenol is now synthesized on a commercial scale as follows:



2. DOW PROCESS:



3. RASCHIG PROCESS:



Phenol is often called carbolic acid, and this terminology is derived from its weakly acidic properties. Its sodium and potassium salts (sodium and potassium phenolates) are soluble in water.

Phenol occurs as colorless to light pink, interlaced, or separate needle-shaped crystals, or as a white or light pink, crystalline mass that has a characteristic odor. It is soluble 1 to 15 in water, very soluble in alcohol, glycerin, fixed and volatile oils, and is soluble in petrolatum and liquid petrolatum.

Phenol is the most stable member of the group of phenols, although slight oxidation does take place upon exposure to air. It can be sterilized by heat and readily forms eutectic mixtures with a number of compounds such as thymol, menthol and salol. Phenol is readily substituted by bromine to form the insoluble tribromo derivative. (For

other general properties of phenol see p. 149.)

Phenol is one of the oldest antiseptics, having been introduced in surgery by Sir Joseph Lister in 1867. In addition to its bactericidal activity, which is not very strong, it has a caustic and slight anesthetic action. Phenol is, in general, a protoplasmic poison and is toxic to all types of cells. High concentrations will precipitate proteins whereas low concentrations denature proteins without coagulating them. This denaturing activity does not firmly bind phenol and, thus, it is free to penetrate the tissues. The action on tissues is a toxic one and pure phenol is corrosive to the skin, destroying much tissue and may lead to gangrene. Even the prolonged use of weak solutions of phenol in the form of lotions is apt to cause tissue damage and dermatitis.

Phenol is commonly used in $\frac{1}{2}$ to 3 per cent concentrations as an antipruritic in compound calamine lotion or as an ointment or simple aqueous solution. Aqueous solutions stronger than 2 per cent should not be applied to the surface of the body. Pure phenol in very small amounts may be used to cauterize small wounds. A 4 per cent solution in glycerin may be used if necessary. Crude phenol is cheap enough to be used for a disinfectant. Phenol is too soluble and too readily absorbed to be of value as an intestinal antiseptic.

OFFICIAL OCCURRENCE	PER CENT PHENOL
U.S.P.	
Phenol Ointment	2.0
N.F.	
Aromatic Spray	2.0
Phenolated Calomine	
Lotion	1.0
Phenolated Iodine Solution.	0.6
Phenolated Neocalomine	
Lotion	1.0
Camphorated Phenol	30.0
Phenol Glycerite	20.0
Phenolated Oil	5.0
Phenolated Water	2.2
Compound Sodium Borate	
Solution	0.3
Compound Zinc Sulfate	
Powder	0.1

The bactericidal activity of most sub-

stances has been compared to Phenol U.S.P. as a standard, and this activity is reported as the phenol coefficient.¹ The phenol coefficient is defined as the ratio of the dilution of a disinfectant to the dilution of phenol required to kill a given strain of a definite micro-organism, *Eberthella typhosa*, under carefully controlled conditions in a specified length of time. For example, if the dilution of the substance undergoing the test is ten times as great as that of phenol, which is the compound used and taken as unity, then the phenol coefficient (P.C.) is ten. This method of testing contains variables that do not permit easy duplication of results by different laboratories; also, for another organism the coefficient may be considerably different.

Almost all phenolic compounds exhibit some antibacterial properties, and this activity is not too specific, although in some cases the phenol coefficient of a given phenol for *Eberthella typhosa* and *Staph. aureus* may differ quite widely.

Because phenol itself is antiseptic, early workers (Ehrlich, 1906, etc.) sought to improve its activity by modifications of its structure. The introduction of the halogens, chlorine or bromine, into the nuclei of phenols increases their antiseptic activities. This activity increases with the increase in the number of halogens introduced, however, the solubility decreases, thus rendering the poly-halogenated phenols much less useful. Furthermore, the halogen derivatives are more toxic and therefore not suitable for internal disinfection. The introduction of nitro groups increases the antiseptic activity to a moderate degree, whereas carboxyl and sulfonic acid groups are ineffective or moderately effective. The introduction of alkyl groups into phenol, cresols, etc. causes a marked increase in antiseptic activity. The structure and size of the alkyl chain exert marked differences in their effects. Normal alkyl chains are more effective than iso-alkyl chains, which in turn are more effective than secondary chains, and the tertiary

chains are the least effective; however, the latter do exert considerable activity. Alkoxy groups also increase the activity of phenols.

Table 15 gives the phenol coefficients of some of the substituted phenols as compared to some of the more well-known antiseptics.²

The alkyl phenols, although powerful antiseptics, are too toxic for internal use and are used for skin sterilization, skin antiseptics and oral antiseptics.

Phenols exert a definite vermicial activity which is enhanced by the presence of alkyl groups. The most effective anthelmin-

TABLE 15. PHENOL COEFFICIENTS OF SOME SUBSTITUTED PHENOLS AND SOME ANTISEPTICS*

COMPOUND	ORGANISM		
	<i>E. typhosa</i>	<i>Staph. aureus</i>	<i>Strep. hemolyticus</i>
Phenol	1.0	...	...
2-Chlorophenol	3.6	3.8	...
2-Bromophenol	3.8	3.7	...
3-Chlorophenol	7.4	5.8	...
4-Chlorophenol	3.9	3.9	...
4-Bromophenol	5.4	4.6	...
2,4-Dichlorophenol	13.0	13.0	...
2,4-Dibromophenol	19.0	22.0	...
2,4,6-Trichlorophenol	23.0	25.0	...
<i>p</i> †-Methyl Phenol	2.5§	...	...
<i>p</i> -Ethyl Phenol	7.5§	10.0	...
<i>p-n</i> -Propyl Phenol	20.0§	14.0	...
<i>p-n</i> -Butyl Phenol	70.0§	21.0	...
<i>p-n</i> -Amyl Phenol	104.0§	20.0	...
<i>p-n</i> -Hexyl Phenol	90.0§	...	...
Thymol	...	28.0	...
Carvacrol	...	28.0	...
4-Ethylmetacresol‡	12.5§	...	...
4- <i>n</i> -Propylcresol	34.0§	...	...
4- <i>n</i> -Butylcresol	100.0§	...	...
4- <i>n</i> -Amylcresol	280.0§	...	...
4- <i>n</i> -Hexylcresol	275.0§	...	...
<i>p</i> -Methyl- <i>o</i> -chlorophenol	6.3	7.5	5.6
<i>p</i> -Ethyl- <i>o</i> -chlorophenol	17.3	15.7	15.0
<i>p-n</i> -Propyl- <i>o</i> -chlorophenol	38.0	32.0	35.0
<i>p-n</i> -Butyl- <i>o</i> -chlorophenol	87.0	94.0	89.0
<i>p-n</i> -Hexyl- <i>o</i> -chlorophenol	...	714.0	625.0
<i>p-n</i> -Amyl- <i>o</i> -chlorophenol	80.0	286.0	222.0
<i>o-n</i> -Amyl- <i>p</i> -bromophenol	63.0	571.0	...
<i>p</i> -Hydroxyphenyl- <i>n</i> -amyl sulfide	75.0	150.0	...
<i>p</i> -Hydroxyphenol- <i>n</i> -amylether	29.0	30.0	...
Lysol	5.0	...	...
Picric acid (2-3%)	5.8	...	...
Merthiolate	40.0	...	...
	50.0		
Metaphen	1,500.0	...	...
Mercurochrome	1.7	...	...
Iodine (3% Tr.)	5.8	...	...
Hydrogen peroxide	0.01	...	...
Dakin's solution	0.78	...	...
Chloramine T	100.0	...	...

* After Suter, C. M.: Chem. Rev. 28:269, 1941.

† Position shown to be unimportant.

‡ The 4-alkylorthocresols and the 2-alkylparacresols assay much like the 4-alkylmetacresols.

§ 20° C.

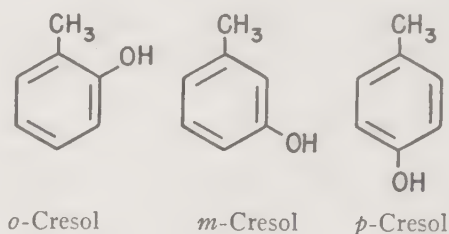
|| 25° C.

tics in this group must have a solubility in water of a relatively low order (1:1,000 to 1:2,000) so as to prevent too great absorption from the stomach and intestines.

Phenols and their derivatives have anti-septic, anthelmintic, anesthetic, keratolytic, caustic, vesicant and protein precipitant properties. The extent of activity in any one or more of the above properties, varies with the type of phenol, i.e., mono, di and tri-hydroxy substitution and with the type and extent of substitution, i.e., alkyl, alkoxy, acetoxy, halogen, nitro, sulfonic, etc. groups.

As a rule, phenols are inactive in the presence of serum, possibly because they combine with serum albumin and serum globulin and, thus, are not free to act upon the bacteria. A second undesirable feature of phenols for blood stream infections, etc. is the inhibitory effect upon leucocytic activity as compared to their activity to inhibit bacterial growth. Table 16 shows these relationships of phenol compared with some of the well-known bactericidal and bacteristatic agents.³

jected to fractional distillation, and the three isomeric hydroxytoluenes are obtained as one fraction because they are not readily resolved into pure entities.



Cresol is a colorless, yellowish to brownish-yellow or pinkish, highly refractive liquid that has a phenol-like, sometimes empyreumatic odor. It is soluble in alcohol or glycerin, and 1 cc. is soluble in 50 cc. of water.

By virtue of the methyl groups, the cresols have a P.C. for *E. typhosa* of about 2.5. It supplies the need of a cheap antiseptic and disinfectant and it is a constituent of Saponated Cresol Solution U.S.P. Because one gram of cresol is soluble only in 50 cc.

TABLE 16. PHENOL COMPARED WITH SOME WELL-KNOWN BACTERICIDAL AND BACTERISTATIC AGENTS*

ANTISEPTIC	LEAST CONC. NECESSARY TO INHIBIT GROWTH OF BACTERIA IN BLOOD.	LEAST CONC. NECESSARY TO INHIBIT LEUCOCYTIC ACTIVITY.	LEUCOCYTE BACTERIA RATIO.
Phenol	1:320	1:1,280	1/4
Eusol	1:2	1:8	1/4
Acriflavine	1:100,000	1:500,000	1/5
Mercuric Chloride	1:2,500	1:20,000	1/8
Cetavlon	1:60,000 <i>Staph.</i>	1:2,000	30
Sulfanilamide	1:200,000 <i>Strep.</i>	1:200	1,000
Penicillin	1:50,000,000 <i>Strep.</i>	1:100	500,000

* After Fleming, A.: Chem. & Ind. 18, 1945.

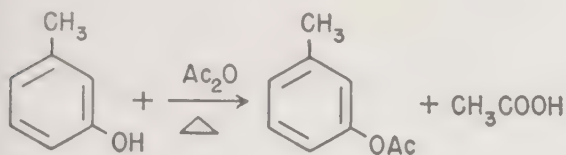
MONO-*p*-CHLOROPHENOL is used in combination with camphor in liquid petrolatum for intratracheal instillation in acute chronic laryngitis, tracheitis and tracheobronchitis.

Cresol U.S.P. Cresol, also called cresylic acid and tricresol, is a mixture of three isomeric cresols obtained from coal tar. The alkali-soluble fraction of coal tar is sub-

jected to fractional distillation, and the three isomeric hydroxytoluenes are obtained as one fraction because they are not readily resolved into pure entities. Cresol is a colorless, yellowish to brownish-yellow or pinkish, highly refractive liquid that has a phenol-like, sometimes empyreumatic odor. It is soluble in alcohol or glycerin, and 1 cc. is soluble in 50 cc. of water. By virtue of the methyl groups, the cresols have a P.C. for *E. typhosa* of about 2.5. It supplies the need of a cheap antiseptic and disinfectant and it is a constituent of Saponated Cresol Solution U.S.P. Because one gram of cresol is soluble only in 50 cc. of water, it is emulsified to the extent of 50 per cent in this preparation by the potassium soaps of vegetable oils. This stock solution can be diluted with water to give a solution, colloidal suspension or emulsion of cresol of the desired strength. Cresol may be used as a 2 per cent solution to disinfect the hands. A 1:500 dilution of saponated

cresol solution sometimes is used as a mildly antiseptic vaginal douche.

Meta-Cresylacetate (Cresatin) N.N.R. is the acetyl ester of *m*-cresol. It can be prepared by heating *m*-cresol with acetic anhydride.

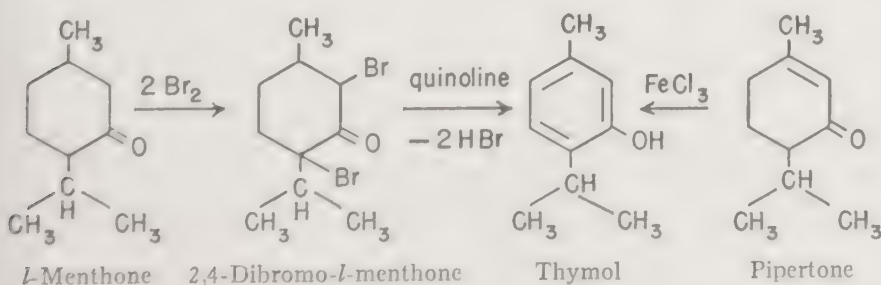


Meta-cresylacetate occurs as a colorless oily liquid, possessing a characteristic odor. It is practically insoluble in water, but it is soluble in the ordinary organic solvents, in liquid petrolatum (not over 5 per cent) and in fixed and volatile oils.

The acetylation of the phenolic group in *m*-cresol produces a compound that slowly liberates the free phenol upon contact with tissues. This property lowers the toxicity and corrosive action of *m*-cresol so that it can be used for the treatment of infections of the nose, throat and ear.

Meta-cresylacetate may be used pure or in solution in alcohol or oils.

Thymol U.S.P. Thymol or thyme camphor is isopropyl *m*-cresol. It is prepared from the oil of thyme (*Thymus vulgaris*) by extraction with alkali and subsequent acidulation of the alkaline extract to liberate the thymol. It can be distilled to effect further purification if necessary. Thymol also occurs in a number of other plants belonging to the mint family. It can be prepared from *l*-menthone by bromination followed by treatment with quinoline, or by the treatment of piperitone (from Australian eucalyptus oils) with ferric chloride, or from *m*-cresol and isopropyl alcohol or propylene in the presence of a suitable catalyst.



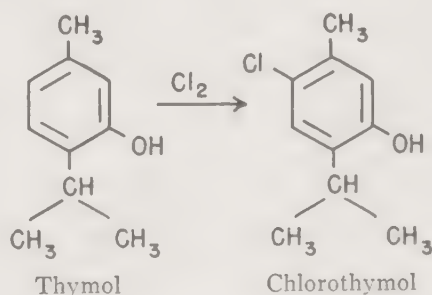
Thymol occurs as colorless, and at times large, crystals, or as a white crystalline powder that has an aromatic, thymelike odor and a pungent taste. It is soluble 1:1,000 in water, 1:1 in alcohol, and is soluble in volatile and vegetable oils.

Although thymol is affected by light, it is quite stable and can be sterilized by heat. It forms eutectic mixtures (see Phenol).

Thymol has fungicidal properties and is effective in controlling dermatitis caused by pathogenic yeasts. It is effective in a 1 per cent alcoholic solution for the treatment of epidermophytosis and in a 2 per cent concentration in dusting powders for ringworm; it can be used both orally and locally for actinomycosis infections. Its use as an intestinal antiseptic is declining in favor of other, superior drugs.

OFFICIAL OCCURRENCE	PER CENT THYMOL
N.F.	
N.F. Antiseptic Solution	0.05
Alkaline Aromatic Solution	0.05
Aromatic Spray	0.10
Kaolin Cataplasm	0.05
Compound Zinc Sulfate Powder	0.10

Chlorothymol (Monochlorothymol) N.F. Chlorothymol is 6-chlorothymol and is prepared by the chlorination of thymol.



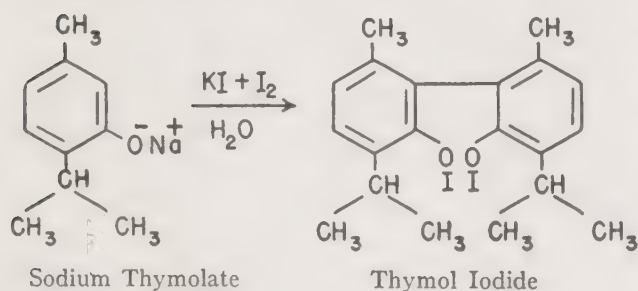
Chlorothymol occurs as white crystals or as a crystalline, granular powder, possessing

a characteristic odor and an aromatic, pungent taste. It is more stable than thymol. One gram dissolves in 0.5 cc. of alcohol whereas it is almost insoluble in water.

It is a very effective antiseptic and is present in Antiseptic Solution N.F. It is used in 2 per cent solutions for wet dressings, in 0.5 per cent solutions for bladder irrigations and in 2 to 5 per cent solutions for disinfection of surgical instruments.

OFFICIAL OCCURRENCE	PER CENT
N.F.	
N.F. Antiseptic Solution.	0.05

Thymol Iodide N.F. (Aristol). Thymol Iodide is a mixture of iodine derivatives of thymol, principally dithymoldiiodide ($C_6H_2CH_3C_3H_7OI$)₂ containing not less than 43 per cent of Iodine. It is prepared by adding a solution of iodine in potassium iodide to a solution of thymol in sodium hydroxide. The thymol iodide separates out almost immediately.



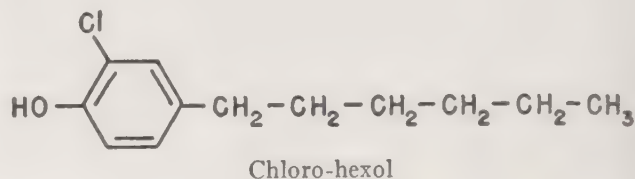
Thymol iodide occurs as a reddish-brown or reddish-yellow, bulky powder, with a very slight, aromatic odor. It is insoluble in water or glycerin, slightly soluble in alcohol and soluble in fixed and volatile oils and in collodion.

Thymol iodide is affected by light and loses iodine upon heating; this reaction is no doubt due to the unstable hypo-iodide structure.

Thymol iodide is used as an antiseptic dusting powder for local application in dermatosis. It can also be used in ointments, oils and collodions.

Chloro-hexol is a water-clear, oily liquid that is insoluble in water but soluble in alco-

hol and acetone. It has a P.C. of 714 against *Staph. aureus* and 625 against *Strep. hemolyticus* and thus finds use as an antiseptic in skin sterilization, cuts, and abrasions and in eye, ear, nose and throat infections.

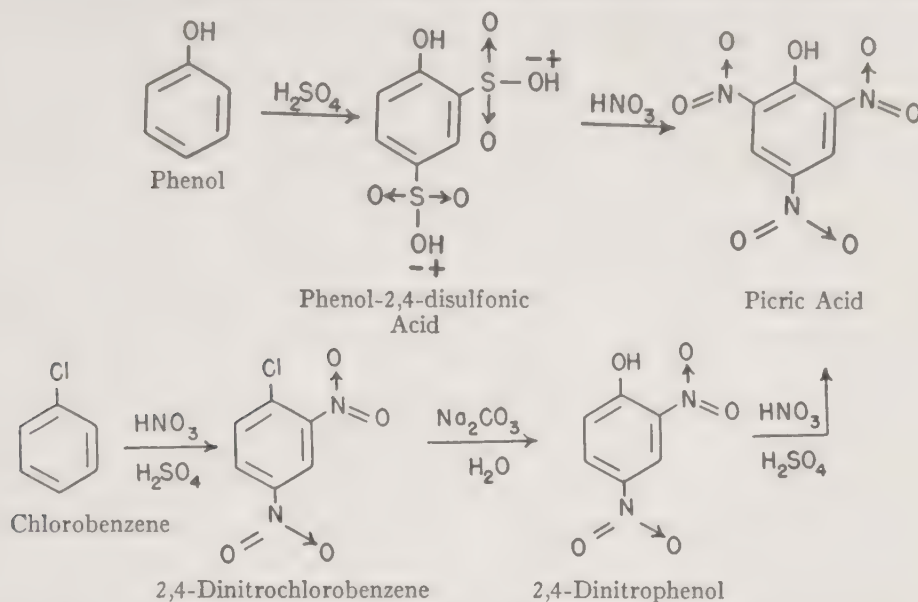


Trinitrophenol (Picric Acid) N.F. is the 2,4,6-trinitro derivative of phenol. It cannot be prepared by the direct nitration of phenol because of the strong oxidizing action of nitric acid upon the readily oxidized phenol. However, it can be prepared as shown in the equations at the top of page 157.

Trinitrophenol occurs as pale yellow prisms or scales that are odorless but have an intensely bitter taste. One gram dissolves in 80 cc. of water and in 12 cc. of alcohol. Because trinitrophenol may explode when heated rapidly or subjected to percussion, it is usually admixed with 10 to 20 per cent of water for safety in transportation. Most, if not all, polynitro compounds are explosive.

Trinitrophenol will decompose carbonates in solution to form the corresponding salt of picric acid. It precipitates proteins, alkaloids, amines and certain aromatic hydrocarbons to form the corresponding picrates. In the case of the nitrogenous substances, these picrates may be looked upon as salts which are not very soluble. It will dye wool and other animal fibers yellow.

Picric acid has a P.C. of 5.9 for *E. typhosa*. This antiseptic activity, together with its ability to form insoluble picrates with proteins and nitrogenous bases, makes picric acid useful in the treatment of burns in 1 per cent solutions. However, the uncombined picric acid may be adsorbed, and large amounts cause toxic effects. It is also present in Butesin (butyl aminobenzoate) picrate, a constituent of an ointment that is



used for the treatment of burns. The Butesin is present for its local anesthetic activity.

Catechol and its Derivatives. Catechol (Pyrocatechin, orthodihydroxybenzene) is a white, crystalline solid that has feeble anti-septic properties, i.e., P.C. for *E. typhosa* 0.87 and 0.58 for *Staph. aureus*. It is not used in medicine as such but some of its derivatives are recognized. These are guaiacol, guaiacol carbonate and eugenol.

Rhus Preparations (Poison Ivy). The N.N.R. recognizes a number of preparations that are essentially solutions in vegetable oils of the purified vesicant principles found in *Rhus toxicodendron*, *Rhus diversiloba* and *Rhus venenata*. The active constituents of these plants is urushiol, and possibly other related compounds that are exceedingly powerful vesicating agents even in very minute quantities. These preparations are injected intramuscularly for either prophylactic or curative measures for poisoning by these ivys. The principle of therapy is supposedly based upon the theory of allergies and their methods of treatment. However, their use appears to be quite irrational and this conclusion is supported in the 1945 Council on Pharmacy Report which is quoted in part as follows: "Ivy extracts whether orally or parenterally administered should be vigorously discouraged in severe

cases of ivy poisoning rashes. Many patients are made worse by such treatment and practice is not in conformity with theory."^{*}

Urushiol and its chemically related vesicating principles are oils that are soluble in alcohol, organic solvents, fixed oils and fixed alkalis. They are precipitated by lead acetate and basic lead acetate but the precipitates, when brought into contact with skin, are apparently fully as effective as the free compounds.⁴

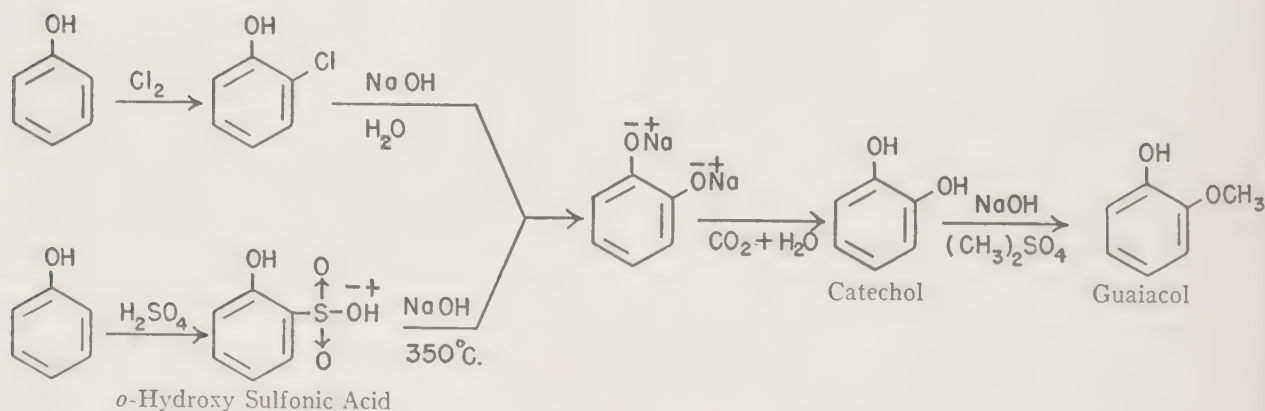
Ferric chloride and cupric acetate each yield a black precipitate with the vesicant principles, and these precipitates are also exceedingly vesicating. Zinc oxide (calamine), aluminum oxide and aluminum subacetate fail to adsorb these phenols. Magnesium oxides (activated) are very effective adsorbents for urushiol and related compounds. However, the resulting adsorbate, if left in contact with the skin, has vesicant properties.⁴ It appears that skin (i.e. protein) will break up these precipitates and adsorbates and form more firmly bound protein complexes. The possibility that the oil of the sweat and sebaceous glands may bring about the same result is not excluded because it appears that these glands are the seat of greatest attack by these vesicants.

^{*} Stevens, F. A.: A. M. A. Council on Pharmacy & Chemistry Reports, p. 86, 1945.

However, organic solvents are not effective in the removal of the vesicants; this would lead one to believe that protein complexes are formed. A logical chemical treatment approach is the use of weak, aqueous or dilute alcoholic alkali (about 1 per cent NaOH) solutions which have proven very effective in actual practice. The alkaline wash can be followed with several rinsings of water. Alkali treatment acts in two ways: (1) it will dissolve the ivy phenols which can be removed by washing with water, (2) the ivy phenols which are like catechol in character are very susceptible to oxidation by air in the presence of alkali. Activated magnesium oxides as dusting powders are valuable adjuvants to the alkaline treatment if they are removed at reasonably frequent intervals.

Sodium hypochlorite solutions are also effective in the treatment of poison ivy.

Guaiacol N.F. is a liquid consisting principally of $C_6H_4(OH)(OCH_3)$ (1:2), usually obtained from creosote, or a solid consisting almost entirely of $C_6H_4(OH)(OCH_3)$ (1:2), usually prepared synthetically as follows:



The term guaiacol is used since the compound is a degradation product of one of the constituents of resin of guaiac.

Liquid guaiacol is colorless or yellowish. Solid guaiacol is crystalline and is colorless or yellowish. Guaiacol is soluble in alcohol, glycerin and one in 60 to 70 cc. of water. Methylation of one of the phenolic groups

in catechol has markedly increased its stability; however, it darkens gradually upon exposure to light.

Guaiacol is a slightly less active antiseptic than phenol, i.e., P.C. for *E. typhosa* is 0.91 and for *Staph. aureus* is 0.73. The corresponding *n*-amyl ether has a P.C. of 22 for *E. typhosa* and 23 for *Staph. aureus*. The mono-alkyl ethers of hydroquinone and resorcinol exhibit the same order of activity as the mono-alkyl ethers of catechol. However, the mono-*n*-hexyl ethers of resorcinol and hydroquinone are more active against *Staph. aureus*, i.e., P. C. 125 and 100 respectively, than the corresponding mono-ether of catechol, P.C. 28.

Guaiacol is used as an intestinal antiseptic with doubtful value. It is also used as an expectorant orally and can be vaporized for inhalation purposes.

The average dose is 0.5 cc.

Guaiacol carbonate is made by condensing guaiacol with carbonyl chloride in the presence of alkali. This ester form of guaiacol is less nauseating and irritating to the stomach and intestines. It is slowly

hydrolyzed in the intestines to liberate guaiacol.

Potassium Guaiacolsulfonate N.F. (Thiocol). "Potassium guaiacol sulfonate, when dried over sulfuric acid for 24 hours, contains not less than 95 per cent of $C_6H_3(OH)OCH_3SO_3K$."

Guaiacol can be sulfonated at 70° to 80°

C. to yield a monosulfonic acid derivative which is converted to the potassium salt.

Potassium guaiacol sulfonate occurs as white crystals or as a white crystalline powder. It has a slightly aromatic odor and a slightly bitter taste. Its aqueous solutions are neutral or alkaline to litmus paper and it is affected by light. One gram of potassium guaiacol sulfonate dissolves in about 7.5 cc. of water at 25° C. It is insoluble in alcohol and in ether.

The introduction of a sulfonic acid group in guaiacol decreases its toxicity and gastro-intestinal irritant effects. Claims for the sedative and expectorant properties of this compound are questionable.

The average dose is 0.5 Gm.

Creosote (Wood Creosote) N.F. Creosote is a mixture of phenols obtained from wood tar. The phenolic fraction of wood tar is recovered in the usual fashion for the separation of phenols from tars. Creosote is composed chiefly of guaiacol, creosol, methyl cresol, etc. These constituents are derived by the pyrolysis of the lignin portion of woody tissue. Lignin is a polymer of 3-methoxy-4-hydroxy benzene (guaiacol) that has a three carbon side chain in position one.

Creosote is an almost colorless or yellowish, highly refractive, oily liquid, having a penetrating, smoky odor and a burning taste. Creosote is slightly soluble in water, but is miscible with alcohol, with ether and with fixed or volatile oils.

Creosote is used for its antiseptic, usually intestinal, anesthetic and expectorant properties.

The average dose is 0.25 cc.

Creosote Carbonate N.F. (Creosotate) is a mixture of the carbonates of various constituents of creosote. It usually is prepared by treating an alkaline solution of creosote with carbonyl chloride. The mixture of esters obtained is first washed with water and finally dried.

Creosote carbonate is a clear, colorless or yellowish, viscid liquid. It is odorless and tasteless, or has a slight odor and taste of

creosote. Creosote carbonate is miscible with alcohol and fixed oils; it is immiscible with water.

Creosote carbonate is used for the same purposes as is creosote. The product causes less gastro-intestinal irritation and nausea than does creosote.

The average dose is 1 Gm.

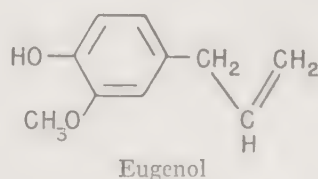
Proposote (creosote phenylpropionate) is prepared by condensing creosote and phenyl propionic acid. The product is amber colored and is used much like creosote carbonate.

Calcium creosotate (Calcreose) is a mixture of the calcium compounds of the constituents of creosote. It is prepared from calcium oxide and creosote. It occurs as a dark brown powder having an empyreumatic odor and a sharp, characteristic, phenolic taste. Calcium creosotate is partially soluble in water; however, on standing it decomposes to yield calcium carbonate and calcium hydroxide.

Calcium creosotate in the solid state or in preparations is claimed to be tolerated better than creosote because it does not readily cause gastric distress and nausea.

Dimol or dimethylmethoxyphenol $C_6H_2(CH_3)_2OCH_3OH$ is used as an intestinal antiseptic in fermentative diarrhea, infantile diarrhea, etc. It is poorly absorbed and passes unchanged in the feces.

Eugenol U.S.P. is a phenol obtained from clove oil and from other sources. Clove oil, which contains not less than 82 per cent eugenol, is extracted with alkali, and the eugenol is subsequently freed from the separated alkaline extract by acidulation. Further purification can be effected by distillation. A number of other volatile oils also contain eugenol.



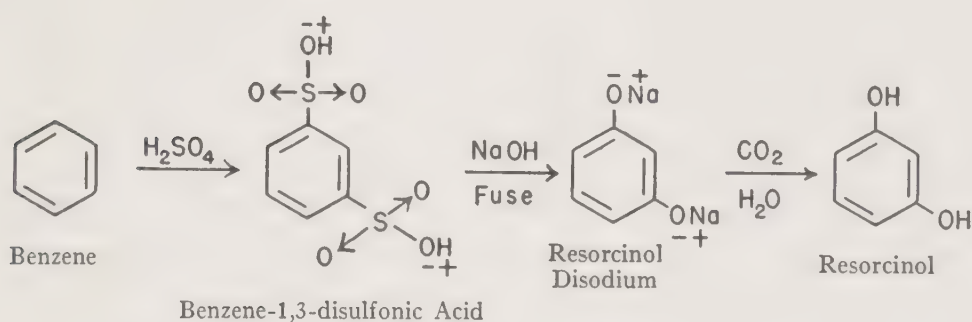
Eugenol is a colorless or pale yellow, thin

liquid, having a strongly aromatic odor of clove and a pungent, spicy taste. It is slightly soluble in water, soluble in twice its volume of 70 per cent alcohol and is miscible with alcohol and with fixed and volatile oils.

The para-allyl and ortho-methoxy groups contribute to the antiseptic and anesthetic activity of the phenolic group, such that eugenol is used for toothaches, lumbago and for its antiseptic activity in mouthwashes.

OFFICIAL OCCURRENCE	PER CENT EUGENOL
N.F.	
N.F. Toothache Drops	about 60
Zinc Compounds and Eugenol Cement	about 8

Resorcinol (Resorcin) U.S.P. is *m*-dihydroxy benzene. It is prepared synthetically as follows:

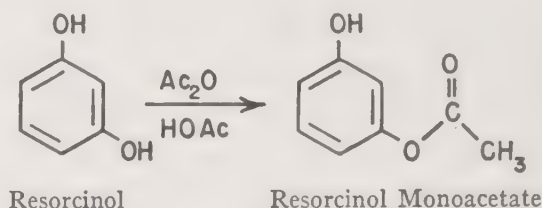


Resorcinol occurs as colorless or nearly colorless, needle-shaped crystals or powder. It has a faint, characteristic odor. One gram is soluble in 0.9 cc. of water, in 0.9 cc. of alcohol, and it is freely soluble in glycerin. Resorcinol should be stored in dark-colored or light-resistant containers. It is much less stable in solution, particularly in the presence of alkaline substances.

Although resorcinol is feebly antiseptic (P.C. = 0.4 for both *E. typhosa* and *Staph. aureus*), it is used in 1 to 3 per cent solutions and in ointments and pastes in 10 to 20 per cent concentrations for its antiseptic and keratolytic action in skin diseases such as ringworm, parasitic infections, eczema, psoriasis, seborrheic dermatitis, etc. Resorcinol has some fungicidal properties.

OFFICIAL OCCURRENCE	PER CENT RESORCINOL
N.F.	
Compound Resorcinol Ointment . . .	6.0
Mild Resorcinol Paste	10.0
Strong Resorcinol Paste	20.0

Resorcinol Monoacetate (Resorcin Acetate) N.F. (Euresol). This compound is prepared by partial acetylation of resorcinol.



Resorcinol monoacetate is a viscous, pale yellow or amber liquid with a faint charac-

teristic odor and a burning taste. It is soluble in alcohol and sparingly soluble in water. Although partial acetylation of resorcinol has increased its stability, it should be stored in tight, light-resistant containers.

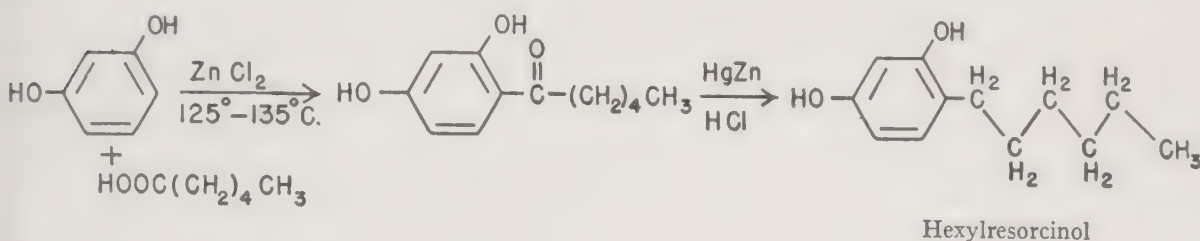
Resorcinol is partially acetylated to produce a milder product with a longer lasting action. The resorcinol monoacetate is slowly hydrolyzed to liberate the resorcinol. It is used in certain skin conditions such as alopecia, seborrhea, acne, sycosis and chilblains.

It is used in 5 to 20 per cent concentrations in ointments and in 3 to 5 per cent alcoholic solutions for scalp lotions.

As a general rule, the esters of phenols are not as stable as the organic esters. They are

very easily hydrolyzed by alkalies or alkaline solutions. They will even hydrolyze very slowly in the solid state in the presence of moisture.

Hexylresorcinol U.S.P. is 4-*n*-hexylresorcinol and is prepared as follows:



In the above synthesis the first step takes place in the presence of anhydrous zinc chloride, and the condensation is of the Friedel and Crafts type. Resorcinol is so readily substituted that an acid, rather than an acid chloride, can be used. Also, because of this ease of substitution, the moderately active zinc chloride provides adequate catalysis. In the second step, a typical Clemmensen reduction, using zinc amalgam and dilute hydrochloric acid, will reduce the ketone to the hydrocarbon.

Hexylresorcinol occurs as white, needle-shaped crystals. It has a faint, fatty odor and a sharp astringent taste; it produces a sensation of numbness when placed on the tongue. It is freely soluble in alcohol, glycerin, vegetable oils, and is soluble 1:2,000 in water. It is sensitive to light.

Although resorcinol is feebly antiseptic, it is less toxic than phenol. This is the basis for the preparation of numerous alkylated resorcinols, the most effective of which was the 4-*n*-hexyl, which has a P.C. of 46 to 56 against *E. typhosus* and 98 against *Staph. aureus*.

Hexylresorcinol was introduced by Leonard and marketed as a 1:1,000 solution under the name of S.T. 37. It was recommended as a general skin antiseptic, being effective for both gram-positive and gram-negative organisms. It can be administered dissolved in olive oil in capsules to be used for an effective urinary antiseptic and an anthelmintic

for *Ascaris* and hookworms. Its low solubility in water makes it an effective anthelmintic; however, sufficient amounts are absorbed to be of value in urinary tract infections.

TABLE 17. PHENOL COEFFICIENTS OF 4-ALKYLRESORCINOLS*

4-ALKYLRESORCINOL	PHENOL COEFFICIENT	
	<i>E. typhosa</i>	<i>Staph. aureus</i>
<i>n</i> -Propyl	5	3.7
<i>n</i> -Butyl	22	10.0
Isobutyl	15	...
<i>n</i> -Amyl	33	30
Isoamyl	24	...
<i>n</i> -Hexyl	46-56	98
Isohexyl	27	...
<i>n</i> -Heptyl	30	280
<i>n</i> -Octyl	0	680
<i>n</i> -Nonyl	0	980

* After Suter, C. M.: Chem. Rev. 28:269, 1941.

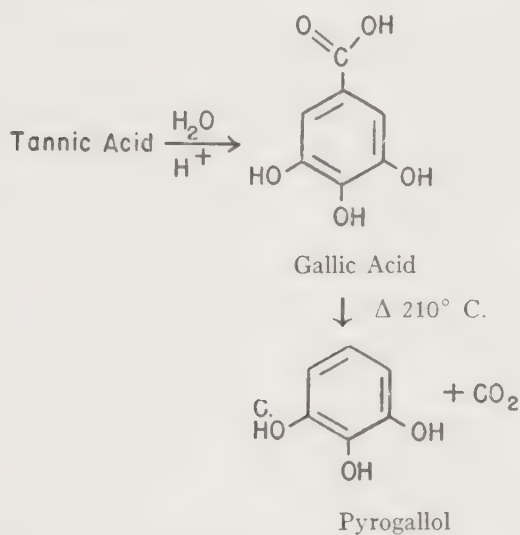
Hexylresorcinol is irritating to the respiratory tract and to the skin, and an alcoholic solution has vesicant properties. This vesicating effect is a general property of alkylated phenols and reaches a very high degree in urushiol.

The alkyl substituted phenols and resorcinols possess the ability to reduce surface tension (see surface-active agents). It is believed that these compounds may owe at least part of their increased bactericidal activity to this ability to lower surface tension because many surface-active agents are very effective germicides.

Hexylresorcinol, like many of the alkyl phenols, exhibits some local anesthetic activity.

The average dose is 1.0 Gm.

Pyrogallol (Pyrogallic Acid) N.F. (Vicinal-trihydroxybenzene or 1,2,3-Trihydroxybenzene). It is prepared by heating gallic acid, which, in turn, is obtained by the hydrolysis of tannic acid. This property of decarboxylation is common to the polyhydroxylated benzoic acids. The ease with which this decarboxylation takes place is dependent upon the number of hydroxyl groups present. The greater the number of hydroxyl groups, the more easily decarboxylation takes place.



Pyrogallol occurs as light, white or nearly white, odorless leaflets or fine needles. One gram is soluble in 2 cc. of water and in 1.5 cc. of alcohol. Pyrogallol when in solution and exposed to air turns brown and acquires an acid reaction due to oxidation by oxygen of the air. If an aqueous solution is rendered alkaline, it can be used in gas analysis to absorb oxygen. It is a strong reducing agent and is used in photography and in engraving.

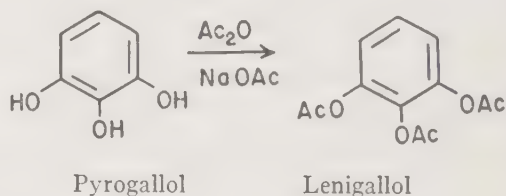
Although pyrogallol is feebly antiseptic (P.C. negligible for *E. typhosa* and *Staph. aureus*), it is used as an antipruritic, irritant, caustic and keratolytic in ringworm, parasitic diseases, psoriasis, lupus, chronic lichen simplex, trichophyton infections and chronic scalp eczema. As such it is used up to 20 per cent concentrations in ointments. Pyrogallol stains the skin, and these stains can be removed by lemon juice, sodium bisulfite or

oxalic acid. Pyrogallol has been used in certain hair dyes.

Pyrogallol should not be used on extensive broken areas of the skin because it may be absorbed in quantities sufficient enough to prove toxic. If absorbed, pyrogallol will cause necrosis of the liver and kidneys and will destroy red blood cells.

Eugallol is pyrogallol monoacetate. It is prepared by the partial acetylation of pyrogallol. This partial acetylation permits a slow liberation of pyrogallol and produces a milder product with a longer lasting action. It is used much the same as pyrogallol and is marketed as a 67 per cent solution in acetone. (See resorcinol monoacetate.)

Lenigallol (Triacetyl Pyrogallol) N.N.R. This compound is prepared by the acetylation of pyrogallol with acetic anhydride and sodium acetate.



Lenigallol is a white crystalline powder that is insoluble in water or alcohol. One gram is soluble in 33 cc. of acetone and in 50 cc. of vegetable oils.

The acetylation of pyrogallol produces a milder product with a longer lasting action due to the slow liberation of pyrogallol. It is used for children in 1 to 20 per cent ointments (chiefly 6 per cent) usually with zinc oxide for the same purposes as pyrogallol. It is also used as a saturated solution in acetone. Acetylation of pyrogallol also reduces the rate of absorption and thus reduces the toxicity.

Gallic Acid is obtained by the hydrolysis of tannic acid. It occurs as white or pale fawn-colored, silky, interlaced needles, or in triclinic prisms. It has an astringent, slightly acidulous taste. One gram of gallic acid is soluble in 87 cc. of water, in 4.6 cc. of alcohol or in 10 cc. of glycerin.

Gallic acid exhibits chemical and medicinal properties similar to those of Pyrogallol of the N.F. Although it precipitates gelatin from aqueous solutions, it does not coagulate albumin. Its astringent action, when it is used in diarrhea, is more mild than that of tannic acid.

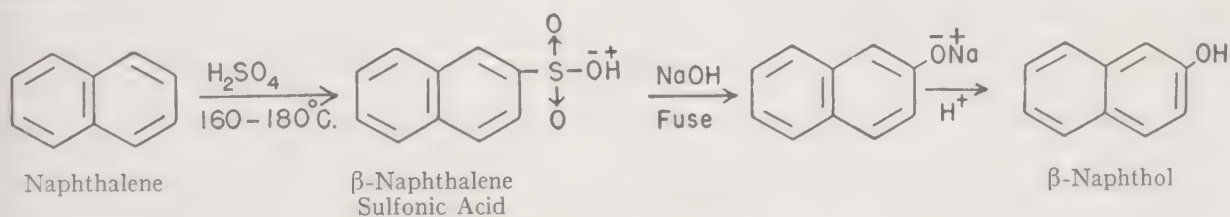
Bismuth Subgallate (Dermatol) N.F. "is a basic salt which, when dried at 105° C. for 3 hours, yields not less than 52 per cent and not more than 57 per cent of Bi₂O₃. Bismuth subgallate occurs as an amorphous, bright yellow powder. It is odorless and tasteless. It is stable in air, but is affected by light." Bismuth subgallate is nearly insoluble in water and in alcohol.

Bismuth subgallate will be decomposed by alkalies, alkali carbonates or mineral acids.

It is used in the treatment of dysentery and diarrhea. The antiseptic action of bismuth is combined with the astringent action of gallic acid.

The average dose is 1 Gm.

Betanaphthol U.S.P. is betahydroxy naphthalene and is prepared synthetically as follows:



Betanaphthol occurs as pale buff-colored, shining crystalline leaflets or as a white or yellowish-white, crystalline powder. One gram is soluble in 1,000 cc. of water or in 0.8 cc. of alcohol. It is soluble in glycerin and olive oil. It has a faint, phenol-like odor and is stable in air.

Betanaphthol, because of its low solubility in water, is not readily absorbed from the intestinal tract. It is used as an intestinal antiseptic and is more safe for internal medication than alphanaphthol, which is more toxic. Nevertheless, betanaphthol is toxic in larger doses and, even though it is effective against the hookworm, other drugs are supe-

rior. When used for hookworms, it is used in conjunction with purgatives.

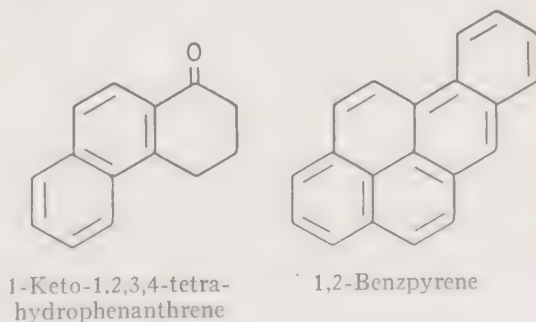
When applied locally, betanaphthol has irritant, corrosive, germicidal, fungicidal, paraciticidal and some local anesthetic activity. Five or 10 per cent concentrations in ointment form are usually employed for the treatment of ringworm, psoriasis and pediculosis.

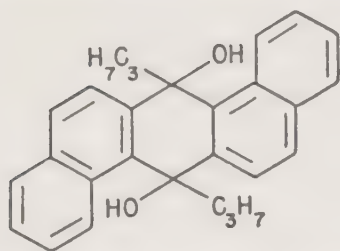
The average dose as an intestinal antiseptic is 0.12 Gm.

SYNTHETIC ESTROGENS

Because estrone contained a polycyclic structure, a keto and a phenolic hydroxyl group, Dodds and co-workers⁵ synthesized a number of polycyclic compounds that contained a ketone and/or a hydroxyl group. 1-Keto-1,2,3,4- tetrahydrophenanthrene had definite estrogenic activity and was the first compound of known chemical constitution to possess such activity.⁵ It was soon discovered that a relatively wide range of such type compounds had some estrogenic activity even though some were hydrocarbons.

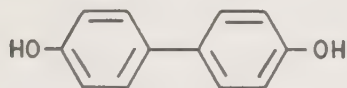
1,2- Benzpyrene, a potent carcinogenic compound, had estrogenic activity, and 9,10- di-*n*-propyl - 9,10- dihydro-1,2,5,6-dibenzanthracene-9,10-diol was more active than estrone.⁶



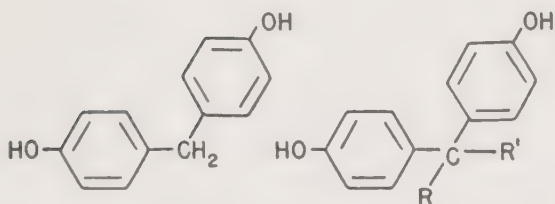


9,10-Di-*n*-propyl-9,10-dihydro-1,2,5,6-di-benzanthracene-9,10-diol

These results were followed by attempts to determine which portions of the molecule were responsible for the estrogenic activity. It was shown that the phenanthrene nucleus was not necessary and that estrogenic activity of a low order was demonstrated in the following type compounds: *p,p'*-dihydroxydiphenyl, *p,p'*-dihydroxydiphenyl methane, di- (*p*-hydroxyphenyl) -alkyl or dialkyl methane, 4,4' - dihydroxybenzophenone and the naturally occurring substance phloretin.⁷ Furthermore, activity was present to a lesser degree in compounds that had only one

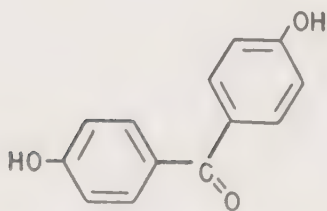


p-p'-Dihydroxydiphenyl

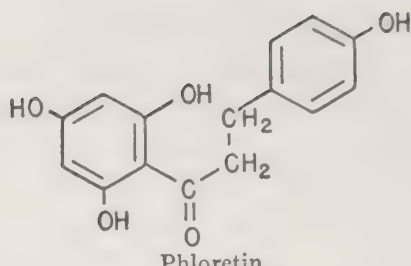


p-p'-Dihydroxydiphenyl Methane

Di- (*p*-hydroxyphenyl) -alkyl or Dialkyl methane where R=CH₃, Et or Pr and R' = H or CH₃.



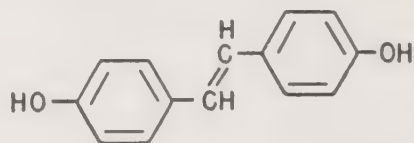
4,4'-Dihydroxybenzophenone



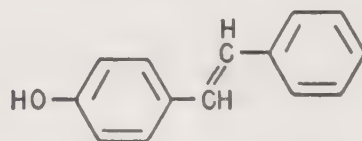
Phloretin

phenolic hydroxyl group, i.e., 4-hydroxyphenylcyclohexane.⁸

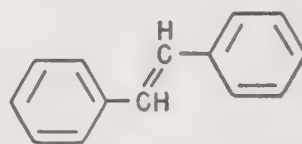
Extension of these studies led to the preparation of 4,4' -dihydroxystilbene, 4-hydroxystilbene and stilbene, which produced full estrus response in castrated mice in 10, 10, and 25 mg. doses, respectively. The two former compounds were, therefore, 10



4,4'-Dihydroxystilbene



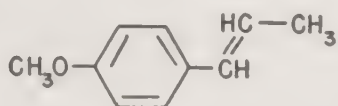
4-Hydroxystilbene



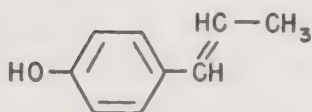
Stilbene

times as active as the above described bisphenolic compounds. Because activity was present in still simpler molecules, such as *p*-hydroxyphenylethyl alcohol, i.e., 100 mg. giving a 60 per cent response, the demethylation of anethole by means of potassium hydroxide was tried in order to prepare a simple phenol with a short unsaturated side chain. This compound, whose structure was supposedly *p*-hydroxy propenylbenzene or anol, exhibited a very high degree of activity. Later it was shown that some batches of anol were highly active while others were not.

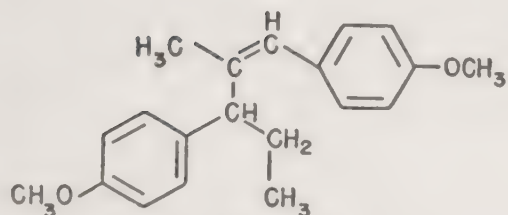
Anol that was completely inactive at the 10 mg. level was converted to a highly active substance when heated for 15 hours at 180 to 200° C. with alcoholic potassium hydroxide.⁹ It was suspected that a polymerized substance was the active product, and the demethylation of di-anethole with potassium hydroxide yielded di-anol, which gave a 100 per cent response in castrated female mice at the 100 microgram level.¹⁰



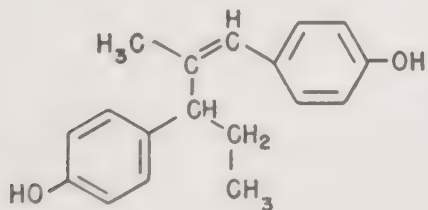
Anethol



Anol

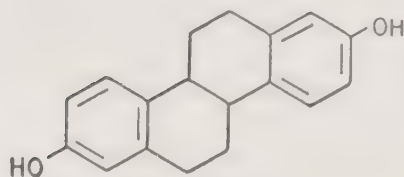
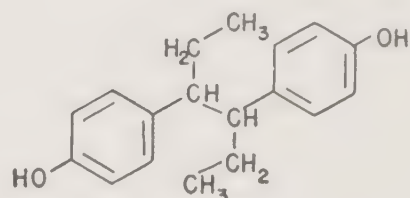


Di-anethole

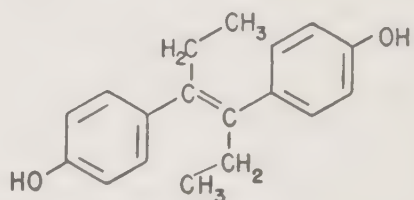


Di-anol

These and other studies stimulated efforts to prepare estrogenic compounds bearing a close relationship to estrone (whose structure was now known), but which would be capable of ready synthesis. These studies culminated in the synthesis of diethylstilbestrol, hexestrol and dihydroxyhexahydrochrysene.¹¹

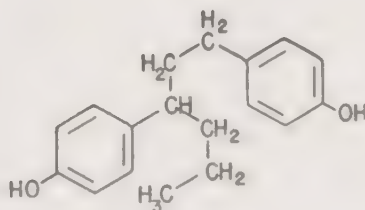
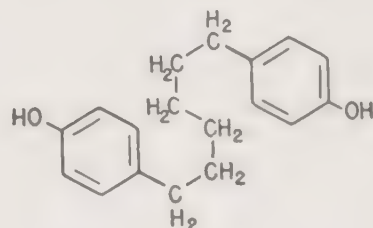

 Dihydroxyhexahydrochrysene
(Active at the 1 mg. level)


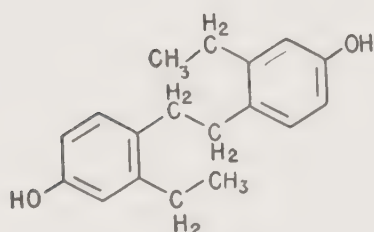
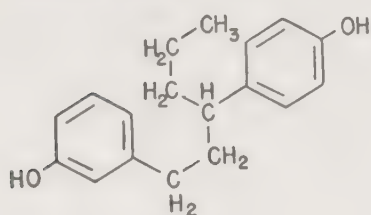
Hexestrol


 Diethylstilbestrol
(Active at 0.3 and 0.4 microgram levels)

Later¹² it was shown that hexestrol could be found in the products obtained by the heating of anol with potassium hydroxide; this accounts for the marked activity obtained.

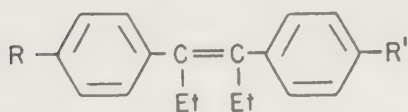
Studies have shown that the following compounds, whose structures can be depicted as being related structurally to estrone, have little if any estrogenic activity.¹³





Hundreds of compounds have been prepared involving many variations in structure. Some of these have marked estrogenic activity, e.g., Benzestrol¹⁴ N.N.R. (Octofollin) and 2-(*p*-hydroxyphenyl)3-methyl-4- (or 6)hydroxyindene.¹⁵ The latter compound is active at the 0.2 to 0.5 microgram level in rats. Table 18 shows the estrogenic activities of some functional variants of diethyl stilbene.¹⁶

TABLE 18. ESTROGENIC ACTIVITIES OF SOME FUNCTIONAL VARIANTS OF DIETHYL STILBENE*



R	R'	ACTIVITY† IN MICROGRAMS
HO	HO	0.3
HO	OCH ₃	2.5
HO	NH ₂	7.5
HO	Br	100.0
OCH ₃	NH ₂	1,000.0
OCH ₃	Br	1,000.0
OCH ₃	COOH	Inactive at 1,000
H	H	Inactive at 1,000

* After Rubin, M., and Wishinsky, H.: J. Am. Chem. Soc. 66:1948, 1944.

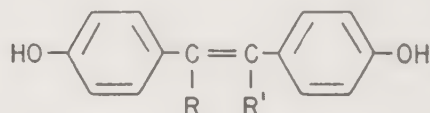
† These weights are equivalent to one rat unit as assayed by the Allan-Doisy method.

Some of the above compounds have been tested for their antiseptic activities which were expressed as the minimum concentrations that prevent growth, after 48 hr. incubation, of the F. D. A. 209 strain of *Staphylococcus*.

R	R'	CONCENTRATIONS
HO	H	1:640,000
HO	Br	1:1,000,000
HO	NH ₂	1:100,000
H	H	1:10,000

Table 19 shows the relationship between activity and the varying alkyl groups in *p,p'*-dihydroxystilbene.¹⁷

TABLE 19. RELATIONSHIP BETWEEN ACTIVITY AND ALKYL GROUPS IN *p,p'*-DIHYDROXYSTILBENE*



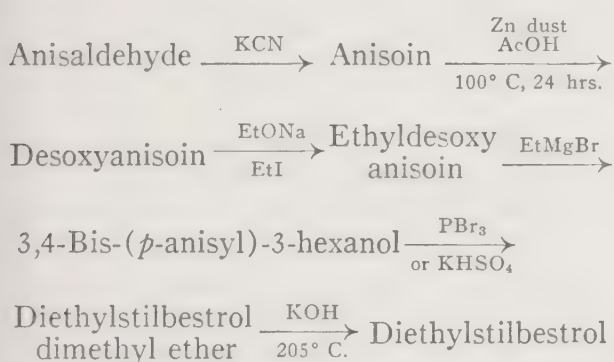
R	R'	DOSE IN MICROGRAMS	PER CENT RESPONSE IN OVARIECTOMIZED RATS
H	H	5,000.0	80
		10,000.0	100
H	Ethyl	100.0	50
Methyl	Methyl	20.0	80
		30.0	100
Methyl	Ethyl	0.5	30
		1.0	100
Ethyl	Ethyl	0.3	80
		0.4	100
Ethyl	<i>n</i> -Propyl	1.0	trace
		10.0	100
<i>n</i> -Propyl	<i>n</i> -Propyl	10.0	75
		100.0	100
<i>n</i> -Butyl	<i>n</i> -Butyl	10.0	0
		100.0	40
Monohydroxy diethylstilbene		100.0	trace
		1,000.0	100

* After Dodds, E. C.: Nature 142:34, 1938.

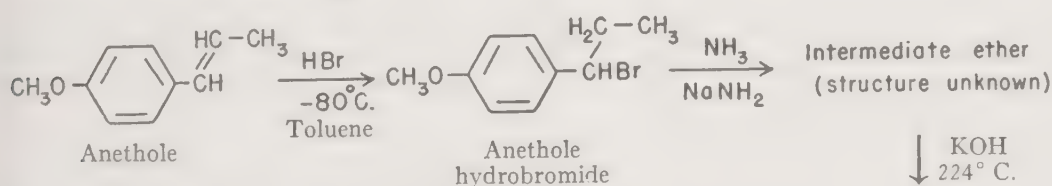
Of a series of esters¹⁸ of diethylstilbestrol the dipropionate gives the maximum prolongation of activity without undue loss in activity. Mono-esters are superior to the more easily prepared diesters.¹⁹

Of a series²⁰ of dialkylated diethylstilbestrols, i.e., methyl to *n*-butyl, the diethyl compound was the most effective, although the activities are decreased very much. The monomethyl ether²¹ was one eighth as active as the free compound.

Diethylstilbestrol (Stilboestrol) U.S.P. The term stilbestrol was suggested for 4,4'-dihydroxystilbene because it is the parent substance of a series of estrogenic agents. Diethylstilbestrol was first prepared by Dodds²² as follows:



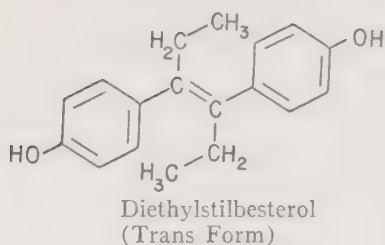
Because of the marked interest in this highly successful estrogenically active compound, it has been prepared in a number of ways, one of which involved a three step synthesis as follows:²³



Diethylstilbestrol occurs as a white, odorless, crystalline powder. It is almost insoluble in water and is soluble in alcohol, chloroform, ether, fatty oils or dilute alkali hydroxides.

Because diethylstilbestrol is a phenol, it exhibits the stability properties of the phenols in general.

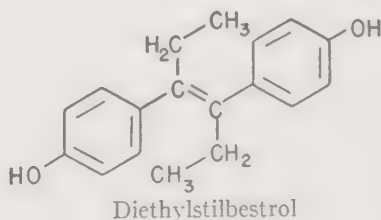
Diethylstilbestrol can exist in a *cis* or *trans* form. The *trans* form or *trans*-4,4'-dihydroxy- α,β -diethylstilbene is more active than the lower melting *cis* isomer, m.p. 142° C. The official drug is the *trans* form, m.p. 169-172° C.



Diethylstilbestrol when administered orally produces hormonelike effects comparable to those produced by the injection of the natural estrogens. It is not inactivated by the liver as are the natural estrogens. It also can be administered subcutaneously or by implantations in the form of pellets.

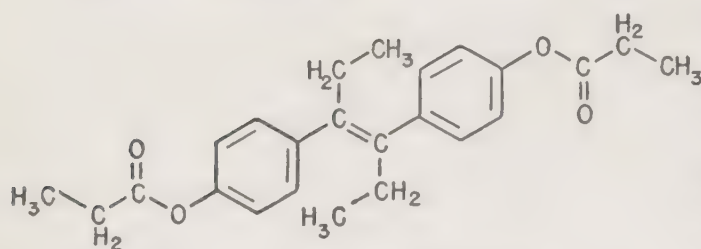
The unpleasant symptoms (in some cases) that arise from the use of diethylstilbestrol are apparently systemic in origin rather than a local effect, probably because of its rapid absorption into the blood stream, since few untoward symptoms are observed with the use of diethylstilbestrol derivatives which are slowly absorbed from the site of administration.

The unpleasant side reactions of the stilbene derivatives are nausea, vomiting and headache.



The average dose is 0.5 mg.

Diethylstilbestrol Dipropionate N.N.R. This ester of *trans*-diethylstilbestrol can be prepared in the usual way for the preparation of esters of phenols.

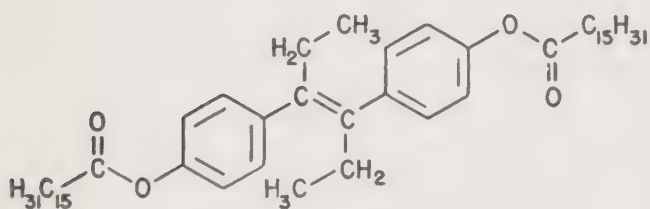


Diethylstilbestrol Dipropionate

Diethylstilbestrol dipropionate is more slowly absorbed than diethylstilbestrol. Therefore, a more prolonged estrogenic effect can be obtained, accompanied by fewer side reactions.

The average dose is 0.5 to 2 mg. two or three times a week.

Stilpalmitate (Diethylstilbestrol Dipalmitate) N.N.R.* Stilpalmitate can be prepared in the usual way for the preparation of esters of phenols.



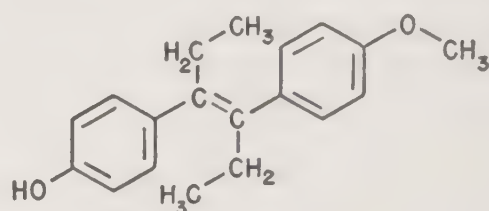
Stilpalmitate

Stilpalmitate occurs as a white to yellowish, odorless, waxy, crystalline powder. It is insoluble in water, slightly soluble in alcohol, sparingly soluble in fatty oils at room temperature, but dissolves more freely on warming. It is soluble in ether and in chloroform.

Diethylstilbestrol dipalmitate is used by intramuscular injection only to produce the prolonged estrogenic effect of diethylstilbestrol accompanied by a reduction of side reactions. Five mg., in terms of diethylstilbestrol, are injected every 5 to 7 days for 3 to 5 doses or until the patient obtains satisfactory relief. Treatment then is discontinued until symptoms recur, at which time the above treatment is repeated until symp-

toms are again relieved. The duration of symptomatic relief between dosage periods will vary from 4 to 12 weeks.

Mestilbol (Monomestrol, Diethylstilbestrol monomethyl ether) N.N.R. Mestilbol is prepared by the methylation of diethylstilbestrol or by the partial demethylation of the dimethyl ether of diethylstilbestrol.



Mestilbol

Mestilbol occurs as an odorless, white, crystalline powder that is insoluble in water and soluble in alcohol, acetone or ether, dilute aqueous solutions of sodium or potassium hydroxide or in vegetable oils. Mestilbol is more stable than diethylstilbestrol.

Monomethylation of diethylstilbestrol has somewhat increased the duration of action and reduced the side effects of diethylstilbestrol. These changes are accompanied by a reduction to $\frac{1}{8}$ of the activity of the parent compound.²⁴

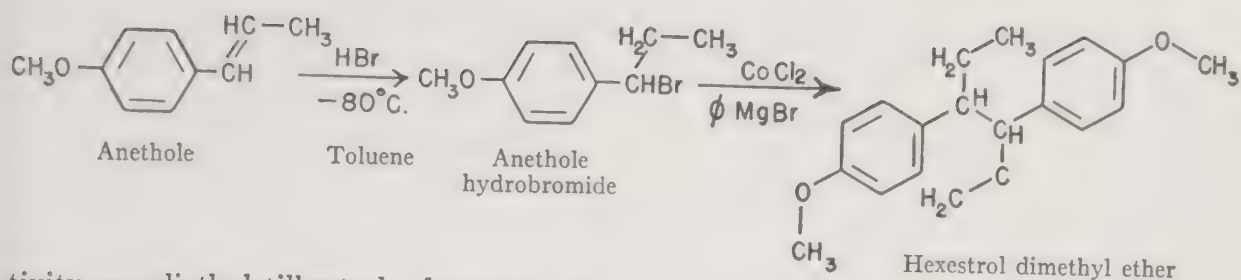
Mestilbol is effective orally and parenterally. The oral dose may range from 0.1 to 5 mg. daily, and the parenteral dose in oil ranges from 10 to 25 mg. biweekly.

Hexestrol (Meso-3,4-di-*p*-hydroxyphenyl-*n*-hexane) N.N.R. Hexestrol originally was prepared by Dodds and co-workers²⁵ by the demethylation of anethole with potassium hydroxide and by the reduction of diethylstilbestrol (see synthesis of diethylstilbestrol). Kharasch and Kleiman,²⁶ by a three step reaction, were able to synthesize hexestrol in good yield. (See the equation at the top of page 169.)

Hexestrol can exist in 3 forms, i.e., *d-l* or the meso forms. The meso form is more effective than the lower melting *dl*-form.

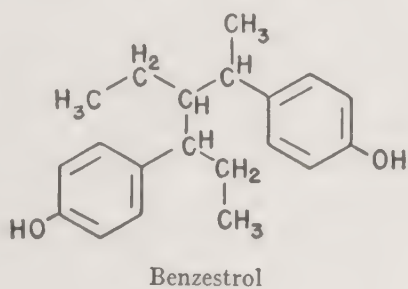
The average dose is 0.2 to 1.0 mg. daily. Hexestrol has about the same order of ac-

* 1947 supplement.



tivity as diethylstilbestrol; however, the claim is made that the incidence of side reactions is lower.

Benzestrol (Octofollin) N.N.R. Benzestrol is 2,4-di-(*p*-hydroxyphenyl)-3-ethylhexane. It was the most active member of a series²⁷ of tri-alkyl derivatives of 1,3-di-(*p*-hydroxyphenyl)-propanes.

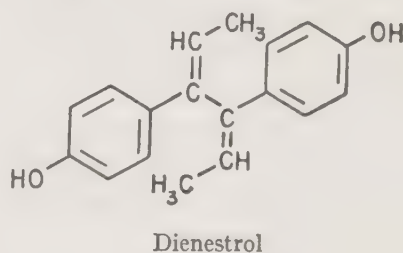
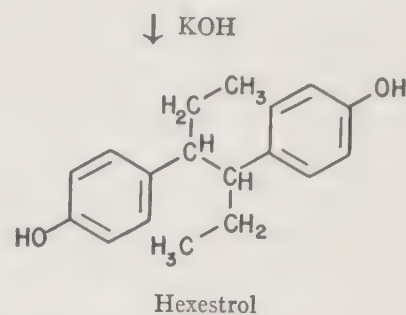


Because benzestrol has three asymmetric carbon atoms, it can exist in 8 possible isomeric forms, one of which is more active²⁸ than the others and is the product official in the N.N.R. This isomer has an estrogenic activity on the order of twice that of estrone when tested in spayed mice and rats.

Benzestrol is used for its estrogenic activity, which parallels that of diethylstilbestrol; however, the claim is made that benzestrol exhibits fewer side reactions.

Benzestrol is orally effective and is administered in 2 to 3 mg. doses daily. Parenterally, it is administered every 5 to 10 days in 2 to 5 mg. doses dissolved in sesame oil.

Dienestrol is 3,4 bis (*p*-hydroxyphenyl) 2,4-hexadiene. It occurs as a crystalline powder that is insoluble in water but readily soluble in alcohol. It is an orally effective estrogen that is claimed to be well tolerated in the dosages recommended, i.e., 0.1 to 0.5 mg. daily.



TANNINS

The term tannin is applied to a group of complex phenolic substances that occur in nature and that exhibit similar physical and chemical properties. A substance is usually classified as a tannin if it fulfills the following requirements.

1. Soluble in water or hydro-alcoholic solutions
2. Soluble in glycerol or propylene glycol
3. Usually they are amorphous in character and their aqueous or alcoholic solutions are colloidal
4. Usually insoluble in petroleum ether, ether or benzene
5. They are astringent to the taste and tissues
6. They are precipitated from aqueous solutions by gelatin, albumin and other proteins

7. They combine with hide to form leather

8. They form precipitates with some alkaloids and some nitrogenous bases

9. Colored solutions are obtained with iron salts

Tannins occur widely distributed in plants. The amount of tannin present in any particular part of a plant may greatly exceed that found in another part of the same plant. Tannins occur abundantly in actively growing parts of the plant, such as buds, immature fruits, root shoots, inner barks, outer barks, galls, etc. The high tannin content of unripe fruits, e.g., choke cherries, persimmons, etc., disappears partially or wholly when the fruit ripens.

Tannins can be roughly classified into two major groups: (1) hydrolyzable tannins and (2) nonhydrolyzable tannins. The members of the first group can be hydrolyzed to simpler molecules by acid, alkali or enzymatic methods, and they usually give a blue to black color with ferric chloride test solution. The nonhydrolyzable tannins usually are precipitated by bromine water, give a green color with ferric chloride and usually contain a phloroglucinol nucleus in part. Many of the nonhydrolyzable tannins polymerize when heated, particularly in the presence of hydrogen ions, to form difficultly soluble red substances which are called "phlobaphenes" or "tannin reds." This type of polymerization can also take place slowly under ordinary conditions. Light catalyzes this reaction. This phenomenon may account for some of the insoluble materials that separate from some tinctures and fluid extracts upon long standing. Many of the unhydrolyzable tannins (phlobatannins) yield red solutions.

Fear²⁹ has shown that, contrary to the generally accepted idea, all alkaloids are not precipitated by tannins. Tannins have no effect whatsoever on aconitine, apomorphine, berberine, betaine and many other alkaloids, whereas, with atropine, cotarnine, emetine,

ephedrine, hydrastine and cocaine hydrochlorides, only a slight opalescence is produced. Fear observed that, if a dilute solution of an alkaloid failed to produce a precipitate with a dilute solution of tannin, no precipitate would be produced by using higher concentrations.

Some of the more carefully characterized hydrolyzable tannins that yield gallic acid on hydrolysis are as follows: gallotannin from nutgalls, acer-tannin from *Acer ginuala*, glucogallin from the Chinese rhubarb and hamameli-tannin from *Hamameli*.

Caffetannin yields quinic and caffeic acids upon hydrolysis. Caffeic acid is 3,4-dihydroxycinnamic acid.

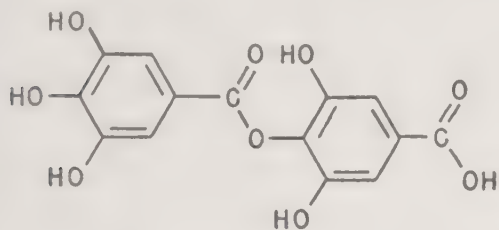
Because the constitutions of the condensed, nonhydrolyzable or phlobatannins are unknown, it is not possible to classify them very readily. Examples of this type of tannin are the tannins found in the barks of the various species of cinchona, wild cherry and most conifers, the best known of which is that found in hemlock. Other examples are the tannins of Indian cutch, cube gambir, rhubarb, hops, tea and the quebrachos.

Tannic Acid (Gallotannic Acid, Tannin) U.S.P. is a tannin usually obtained from nutgall. The gallotannin content of the same and different kinds of galls varies considerably. The average gallotannin content of several commercial varieties of galls follows: Aleppo galls, 58 per cent; Chinese galls, 77 per cent; Bassorah galls, 30 per cent and Morea galls, 30 per cent.

Gallotannin obtained from galls can be purified readily by dissolving it in ethyl acetate and extracting this solution with alkali carbonates to remove any free gallic acid.³⁰ The ethyl acetate then is evaporated to deposit the purified gallotannin.

The constitution of gallotannin is not definitely known. It yields upon hydrolysis, gallic acid in varying amounts, sometimes as high as 100 per cent. Some authors³¹ believe that gallotannin contains glucose and have proposed that gallotannin is a penta-digal-

loyl glucose. Meta-digalloyl residues have been obtained from gallotannin upon hydrolysis by the enzyme tannase.³² Meta-digallic acid has been synthesized.³³ The possibility



m-Digallic Acid

cannot be excluded that gallotannin may be a polygalloyl compound in which the gallic acid residues are esterified to each other, with the terminal carboxyl group in the form of a lactone or coupled with glucose.

Tannic acid occurs as an amorphous powder, as glistening scales or as spongy masses, varying in color from yellowish-white to light brown. It is odorless or has a faint, characteristic odor and a strongly astringent taste. Tannic acid is very soluble in water, in acetone and in alcohol. It is freely soluble in diluted alcohol and slightly soluble in dehydrated alcohol. One gram of tannic acid dissolves in about 1 cc. of warm glycerin.

Tannic acid, because it contains gallic acid residues, is very unstable in the presence of alkalis, alkali carbonates and other basic substances.

Tannic acid is used as a hemostatic, an astringent in diarrhea, in the treatment of *Rhus* dermatitis and in the treatment of burns. Its extensive use in the treatment of burns is based upon its ability to precipitate the dead protein tissue to form an eschar. The protein thus combined is not available as a nutrient for bacteria, and the eschar (tanning effect) furnishes a protective covering which reduces the loss of serum (pressure dressing effect) and prevents external contamination. Five to 10 per cent aqueous tannic acid solutions are applied as a wet dressing or sprayed on the burned areas. Alternate applications of silver nitrate often are used to produce a

heavier eschar. Other antiseptics also are used in conjunction with tannic acid.

One disadvantage claimed for the use of tannic acid therapy is the liver damage that may possibly result from the gallic acid liberated upon the hydrolysis of the tannic acid. This problem would not be encountered if a nonhydrolyzable tannin (phlobatannin) were used. It has been demonstrated in rats that a phlobatannin is much less toxic and equally as effective as tannic acid for burns.³⁴

Acetyltannic Acid (Diacetyltannic Acid, Tannyl Acetate, Acetannin) is a product obtained by the acetylation of gallotannin. The use of this compound in diarrhea is based upon the slow liberation of tannic acid through hydrolysis in the intestines.

Tannic acid has been combined with albumin to form Albumin Tannate and with casein to form a tannin caseinate (Protan). These compounds are used for the same purpose and reasons as described for acetyltannic acid. All these compounds act at all levels in the intestine.

Heliobrom (Urea dibromtannate) is a combination of urea and brominated tannic acid. It is used in alcoholic solutions (10 per cent) and in ointments (5 to 10 per cent) for itching skin lesions, such as pruritus ani and vulvae, urticaria and poison ivy dermatitis.

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14

Aromatic Alcohols, Aldehydes, Ketones, Ethers and Quinones

SATURATED AROMATIC ALCOHOLS
UNSATURATED AROMATIC ALCOHOLS
ESTERS OF AROMATIC ALCOHOLS
AROMATIC ALDEHYDES
AROMATIC KETONES
AROMATIC ETHERS

QUINONES
NAPHTHOQUINONES
ANTHRAQUINONES
ANTHRAQUINONE REDUCTION PRODUCTS

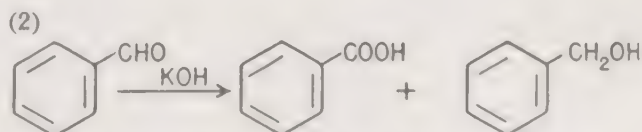
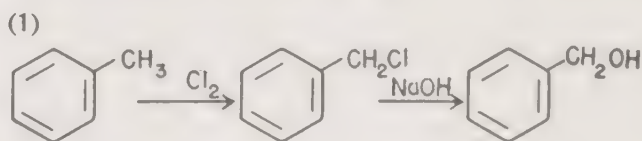
Aromatic alcohols, aldehydes, ketones and ethers are compounds that contain an aromatic nucleus. The simplest alcohols and aldehydes are derivatives of methanol and formaldehyde, respectively. The simplest ketone is acetophenone ($C_6H_5COCH_3$), and the simplest ether is phenylmethyl ether ($C_6H_5OCH_3$). The effect of an aromatic ring on the chemical properties of the alcohol, aldehyde, ketone or ether is pointed out in the discussion of each class. The reactivity of these chemical classes has been mentioned previously in the chapters on aliphatic compounds. Quinones have individual characteristics not similar to those of other aromatic compounds.

SATURATED AROMATIC ALCOHOLS

In general, the presence of an aromatic ring does not alter the chemical properties of the alcohol group.

Benzyl Alcohol (Phenylcarbinol) N.F.

(Phenylmethanol, Phenmethylol). Benzyl alcohol occurs free in nature (Oil of Jasmine, 6 per cent) and is found as an ester of acetic, cinnamic and benzoic acids in gum benzoin, storax resin, Peru balsam and tolu balsam and in some volatile oils (jasmine and hyacinth). In maize, a glucoside of benzyl alcohol is found. It is readily synthesized from toluene (1) and by the Cannizzaro reaction from benzaldehyde (2).



The alcohol is soluble in water (1:25) and in 50 per cent alcohol (1:1.5). It is miscible

with fixed and volatile oils, ether, alcohol or chloroform. Benzyl alcohol is a clear liquid with a faint aromatic odor. As its boiling point is 204.7° C., it can be sterilized easily by boiling without decomposition.

The chemical properties of benzyl alcohol are much the same as those of primary alcohols, since it is phenylmethanol. On oxidation it first yields benzaldehyde and then benzoic acid. It differs from the aliphatic alcohol in being resinified by sulfuric acid, and it does not form the corresponding sulfuric ester. In comparing it with hydroxybenzene (phenol), the introduction of the "CH₂" group destroys the phenolic properties such as the caustic action and the reaction with alkalis or ferric chloride.

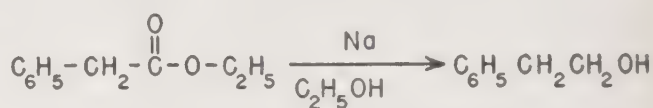
Benzyl alcohol is commonly incorporated as a preservative in ampules of injectible drugs and is also used this way because it exerts a local anesthetic¹ effect when injected or applied on mucous membranes. The concentrations usually employed are 1 to 4 per cent (maximum solubility) in water or saline solution. In such small doses it is non-irritating and nontoxic. Since it is also strongly antiseptic, ointments (lard) containing benzyl alcohol up to 10 per cent are useful in preventing secondary infection and the itching of pruritus and skin conditions. A suitable lotion may be prepared with equal parts of benzyl alcohol, water and alcohol.

Interest in the benzyl group began with the observation that when the isoquinoline ring of the alkaloid papaverine is opened, a β-phenylethyl amine derivative is obtained. Since this secondary amine and its related compounds are useful as antispasmodics, the benzyl group was tried in numerous compounds. Papaverine is a nitrogenous derivative of dimethoxybenzyl. Therefore, other benzyl derivatives have been investigated. Several esters of benzyl alcohol are of value in medicine. The benzyl group, when present in ester form, exerts an antispasmodic² action. In compounds such as the barbiturates, when the benzyl group is placed in position five (5), the opposite effect is pro-

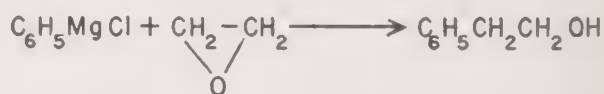
duced, i.e., it shows convulsive³ properties. It is interesting to note that the phenylethyl derivatives of the barbiturates lack the convulsive property of the benzyl compounds.

There are a few other aromatic alcohols of minor importance. For a pharmacologic study of some of these see Hirschfelder.⁴

β-Phenylethyl Alcohol (β- Phenylethylol, Orange Oil or Rose Oil), (C₆H₅CH₂CH₂OH). This compound is useful in perfumery, occurs in oils of rose, orange flowers, pine needles, and Neroli. It is prepared by the reduction of ethyl phenylacetate,



or with phenylmagnesium chloride and ethylene oxide.



This alcohol is slightly soluble in water (2 per cent). It may be sterilized by boiling since it boils at 220° C.

Hjort⁵ found it to be slightly more anesthetic than benzyl alcohol and of the same order of toxicity. It has been used for its stimulant and antispasmodic properties.

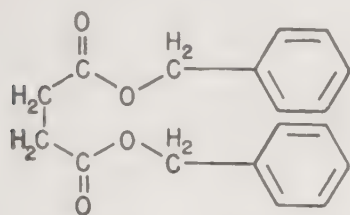
γ-Phenylpropylalcohol (Hydrocinnamyl Alcohol, C₆H₅CH₂CH₂CH₂OH) is found as an ester of cinnamic acid in various balsams and resins (Storax) and can be prepared by the reduction of cinnamyl alcohol. This alcohol has a hyacinthlike odor and, as an ester, is used in perfumes.

UNSATURATED AROMATIC ALCOHOLS

Cinnamyl Alcohol (Styrone, γ-Phenylallyl Alcohol, C₆H₅CH=CHCH₂OH) is found as ethyl cinnamate (Stryacin) in *Storax*. It crystallizes in shining needles, is sparingly soluble in water and possesses a hyacinthlike odor.

ESTERS OF AROMATIC ALCOHOLS

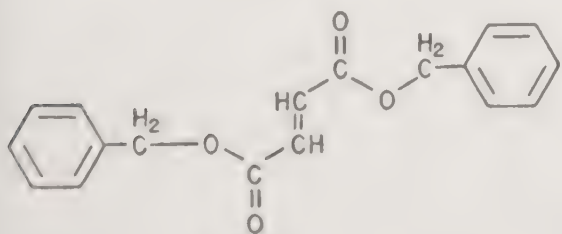
Benzyl Succinate is the dibenzyl ester of succinic acid. It is prepared from succinyl chloride and benzyl alcohol. The ester is a white or faintly yellowish-white, crystalline powder with neither taste nor odor. It is permanent in air. The crystals are soluble in alcohol, ether, chloroform or fixed and volatile oils. It is insoluble in water.



Benzyl Succinate

This compound was developed to make use of the benzyl group as an antispasmodic⁶ (q.v.), and since it is a solid, it eliminated the very disagreeable taste of the liquid esters previously used (benzyl acetate and benzyl benzoate). Benzyl esters are used internally (tablets) for a variety of pathologic conditions, for example, hypertension, angina, asthma, dysmenorrhea and biliary and renal colic, where an antispasmodic is indicated. Clinical studies have revealed that these esters lower the tonus of smooth muscles and are relatively nontoxic. Also, experience has shown that much of the therapeutic claim is unwarranted.

Benzyl Fumarate. The fumarate ester, an odorless, tasteless solid, is prepared in a manner similar to that used for the succinate ester. The solubilities and uses are the same as they are for benzyl succinate (q.v.).

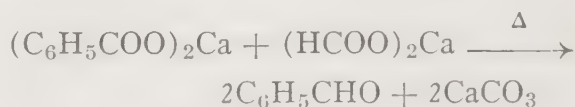


Benzyl Fumarate

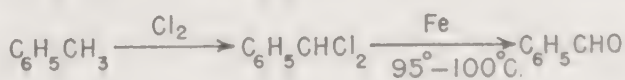
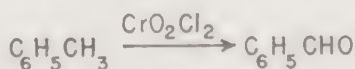
AROMATIC ALDEHYDES

The aryl group of aromatic aldehydes slightly decreases the chemical activity of the carbonyl group when directly attached to it. Its reactivity is less in such reactions as addition, oxidation, condensation and reduction than that of the aliphatic aldehydes (q.v.). Certain reactions that require the presence of bases or acids are possible with those aromatic aldehydes that have no alpha hydrogen atom and hence do not undergo an aldol condensation with themselves (q.v.). Some of these reactions are the Claisen-Schmidt condensation (q.v.), the Perkin reaction (q.v.) and the Claisen reaction.

Benzaldehyde N.F. (Benzoic Aldehyde, Artificial Oil of Bitter Almond). This is the simplest aromatic aldehyde and is found in nature as part of some glycosides, for example, the cyanogenetic glucoside amygdalin (γ - β -gentiobioside of mandelonitrile), which is found in bitter almonds and in the kernels of some fruits (cherry, peach and laurel). It is prepared by methods similar to those used for aliphatic aldehydes (q.v.), e.g., by the oxidation of benzyl alcohol or the distillation of a mixture of calcium benzoate and calcium formate.



Two methods are used for its commercial production, namely, the oxidation of toluene with chromyl chloride (CrO_2Cl_2) or manganese dioxide (MnO_2) and the hydrolysis of benzal chloride with water, using ferric benzoate or powdered iron as a catalyst. The reaction mixture is made basic with calcium oxide and the benzaldehyde is distilled with steam.



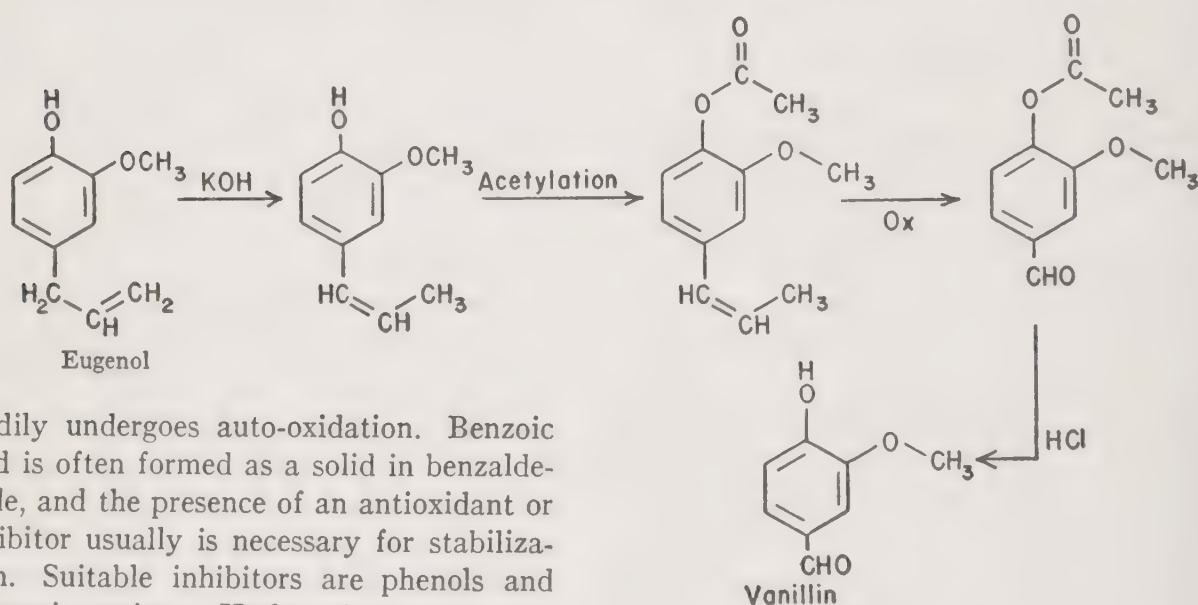
Benzaldehyde is a colorless or yellowish, oily liquid, having a burning taste, an odor similar to bitter almonds. It is affected by light. It is insoluble in water but soluble in organic solvents.

The character of the carbonyl group attached to an aromatic ring is not altered significantly in chemical properties from its character when attached to aliphatic compounds. Benzaldehyde undergoes typical reactions of its class (no alpha hydrogen atom) such as the benzoin condensation (q.v.) and the Cannizzaro reaction (q.v.).

This aldehyde must be stored in well-stoppered bottles protected from light. It

Vanillin U.S.P. (3-methoxy-4-hydroxybenzaldehyde, methyl protocatechuic aldehyde). This aromatic aldehyde occurs naturally in vanilla beans, sugar beets, some balsams and some resins. Vanilla N.F. owes much of its flavoring properties to vanillin. One of the largest sources is from the waste sulfite liquors from the wood pulps and paper industries. Yields as high as 20 to 25 per cent are obtained from spruce lignin and 46 to 48 per cent from maple wood lignin by alkalinitrobenzene oxidation^{7,8} under pressure.

A synthetic method of preparation starting with eugenol is as follows:



readily undergoes auto-oxidation. Benzoic acid is often formed as a solid in benzaldehyde, and the presence of an antioxidant or inhibitor usually is necessary for stabilization. Suitable inhibitors are phenols and aromatic amines. Hydroquinone and nordihydroguaiaric acid have been found to be effective in about 0.001 per cent concentration.

It is employed primarily as a flavor, but has been used as an antispasmodic and as an anesthetic. Large amounts are consumed in the preparation of synthetic pharmaceuticals such as benzoic acid, cinnamic acid, dyes (triphenyl methane dyes), and in photographic work.

Vanillin occurs in fine white-to-yellow crystals, usually needlelike, having a vanilla odor and taste. It is soluble in water (1:100), glycerin (1:200) and organic solvents. Solutions of vanillin are acid and they are affected by light.

The aldehyde group present is responsible for most of the chemical properties of vanillin and is similar in characteristics to that of aliphatic aldehydes (q.v.). It readily forms the bisulfite complex, slowly becomes acid in nature and has the incompatibilities of aldehydes. Due to the presence of the phenolic hydroxyl group, it is soluble in fixed alkalies. Since it is easily oxidized in air to the acid and is volatile at 85° C.,

OFFICIAL OCCURRENCE	PER CENT BENZALDEHYDE
N.F.	
Compound Benzaldehyde Elixir.	0.05
Benzaldehyde Spirit	1.0
Terpin Hydrate Elixir.....	0.005
Terpin Hydrate and Codeine Elixir	0.005

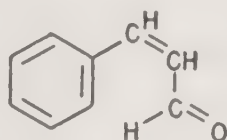
it should be stored in closed containers.

Vanillin is used in large quantities to prepare artificial vanilla extract and as a common flavoring agent. Although present in some tonics and stimulants, no reliable medicinal use has been found.

OFFICIAL OCCURRENCE	PER CENT VANILLIN
U.S.P.	
Liquid Petrolatum Emulsion	0.004
N.F.	
Compound Benzaldehyde Elixir	0.1
Liquid Petrolatum Emulsion with Phenolphthalein	0.004
Compound Vanillin Spirit	0.01
Compound Vanillin Elixir	0.0002
Peptonized Iron and Manganese Solution	0.002
Aromatic Castor Oil	0.1
Aminoacetic Acid Elixir	0.015

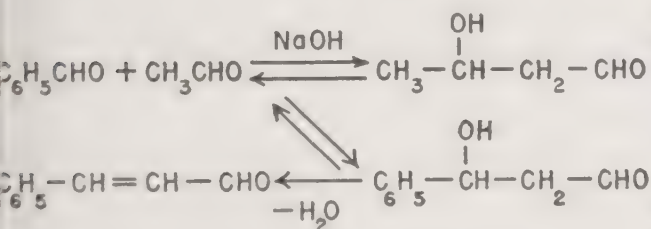
Cinnamaldehyde (Cinnamic aldehyde)

N.F. (Cinnamyl aldehyde, Phenylacrolein).



This aromatic unsaturated aldehyde is found as the primary constituent in oils of cassia and oil of cinnamon. It may be isolated from these oils by the bisulfite addition (q.v.) compound.

Cinnamaldehyde is prepared synthetically by the Claisen-Schmidt condensation, using a mixture of benzaldehyde and acetaldehyde.



It is a yellow, strongly refractive liquid having an odor resembling that of Cassia oil and a burning aromatic taste. This aldehyde is slightly soluble in water (1:700) and miscible with alcohol, ether, chloroform or volatile and fixed oils. It is affected by light.

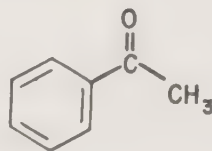
Cinnamaldehyde should be stored in well-

filled, tight containers protected from heat and light. It is similar in reactivity to benzaldehyde (q.v.). Like cinnamon oil, it is used primarily as a flavoring agent.

AROMATIC KETONES

The aromatic ketones, of which acetophenone is the simplest, may have one or two aryl groups associated with a carbonyl group. Chemical properties are the same as those of the aliphatic ketones. These ketones, themselves, are of little use in medicine but may serve as a starting material for other drugs (see hydantoins).

Acetophenone (Phenylmethyl ketone, Hypnone, Acetylbenzene).



This ketone is prepared synthetically and is a clear, stable liquid. It was once used as a hypnotic, but it is a protoplasmic poison affecting the heart, and thus has a high toxicity, with death often occurring. The toxicity increases with the size of the alkyl group (ethylphenyl ketone > methylphenyl ketone).

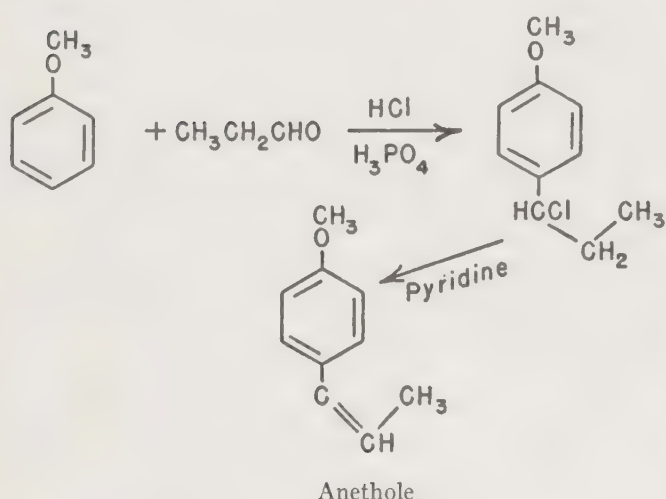
Zingiberone [4-(3-methoxy-4-hydroxyphenyl)-butanone-2]. This ketone contributes to the activity of ginger, while compounds of a similar type are the active ingredients in capsicum.

AROMATIC ETHERS

The aromatic ether structure is present in some pharmaceutical compounds; there are numerous active compounds having alkoxy groups such as methoxy, ethoxy, propoxy, etc. Since the ether structure is usually of secondary importance in most compounds, the classification is based on other groups. (See quinine, guaiacol and eugenol).

Anethole N.F. (Para-methoxypropenylbenzene). "Anethole is para-propenyl ani-

sole. It is obtained from anise oil and other sources, or is prepared synthetically." This aromatic ether is isolated from several volatile oils by fractionating, chilling and crystallizing. It may also be prepared synthetically.⁹



This ether is a colorless or faintly-yellow liquid which congeals at about 20 to 23° C. It has the aromatic odor of anise oil, a sweet taste and the characteristic of being affected by light. It is soluble in organic solvents, but is insoluble in water.

Anethole, when gently oxidized with potassium dichromate, yields anisaldehyde (*p*-methoxybenzaldehyde); on further oxidation, *p*-hydroxybenzoic acid (anisic acid) is formed. Fusion of the ether with potassium hydroxide causes demethylation and the formation of *p*-alphapropenylphenol (anol). The preparation of anol led Dodds¹⁰ to discover hexestrol. Anethole readily adds hydrogen bromide to form anethole hydrobromide. This is a good starting material for the preparation of stilbestrol and hexestrol¹¹ (See Chapter 13).

OFFICIAL OCCURRENCE
N.F.

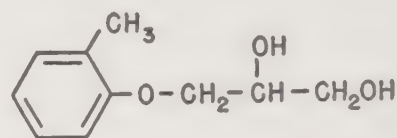
PER CENT
ANETHOLE

Compound Cardamom Spirit.....	0.5
Compound Cardamom Elixir.....	0.005
Anisated Ammonia Spirit.....	3.0

Safrole is the methylene ether of 3,4-dihydroxyallylbenzene and is the main con-

stituent of sassafras oil. It is used for flavoring purposes, as a starting material for the synthesis of piperonal and in the preparation of insecticidal material.

3-*o*-Toloxyl-1,2-propanediol (Myanesin, Tolserol).



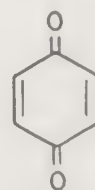
Chemically, the compound is a dihydric alcohol and also an ether. It is a colorless, odorless, crystalline solid, soluble in water to the extent of 1 per cent. Solutions of higher concentration can be obtained by using solubilizing agents such as alcohol, propylene glycol, urea and ethyl urea. In general, the solutions are stable to light, air, cold and dilute acids and bases. Sterilization procedures do not affect the compound and it is stable with solutions containing dextrose, salt or barbiturates.

Tolserol is useful in the treatment of certain neuromuscular disorders including Parkinson's syndrome, cerebral palsy, multiple sclerosis and related spastic conditions. It produces muscular relaxation similar in its superficial aspects to that produced by the curare alkaloids.

QUINONES

Quinones are the product of oxidation of ortho or paradihydroxyaromatic compounds. Resorcinol does not form a quinone.

Para-quinone (1,4-Benzoquinone) is a



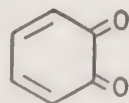
p-Quinone

yellow compound which has a strong pungent odor and colors the skin brown. Some highly-substituted para-quinones have been found in nature as pigments.

In 1932¹² it was found that *p*-benzoquinone and toluquinone were toxic to guinea-pig spermatozoa. Substitution of methoxyl groups¹³ (2,6-dimethoxyquinone) on the ring produced a compound that was antagonistic to the growth of *Staphylococcus aureus*. Replacement of OCH_3 by OH always resulted in decreased activity. Naturally occurring pigments such as fumigatin, spinalosin and phaenecin, found in molds, are related to quinone. Anthelmintic properties have been reported for hydroxybenzoquinones having long chain alkyl groups. An example is embelen (2,5-dihydroxy - 3 - undecyl - 1,4 - benzoquinone), which has been isolated from the berries of *Embelia ribes* and Rapanone (2, 5-dihydroxy-3-tridenyl-1,4-benzoquinone) found in *Rapanea Maximowiczii*. The anthelmintic activity of Male Fern (*Aspidium*, *Dryopteris*, *Filix-mas*) is thought to be due to a complex quinone known as filicinic acid. A series of related compounds were prepared in 1921 by Karrer.¹⁴

In 1948 several derivatives of 1,4-benzoquinone and naphthoquinone were reported as possessing outstanding antifungal qualities.

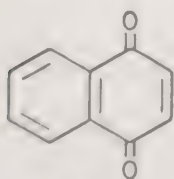
o-Quinone (1,2-Benzoquinone, *o*-Benzoquinone) is the quinone derived by the oxidation of catechol.



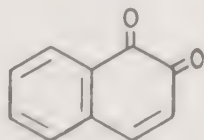
o-Quinone

NAPHTHOQUINONES

Naphthoquinones are of two types, i.e., alpha and beta. Very few derivatives of beta-naphthoquinone have been found in nature and none is of interest in pharmacy.



alpha



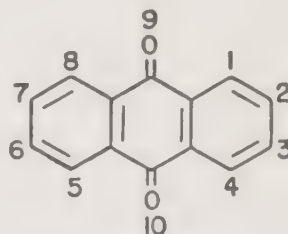
beta

Alpha-naphthoquinone has derivatives that are found in nature and others, prepared synthetically, that are of value in medicine. (See Vitamin K and Menadione). Many of these are pigments such as Lawsone, Juglone, Echinaochrome A and Lapachol, obtained from either plant or animal sources.

ANTHRAQUINONES

Anthraquinone compounds are widely distributed in nature. They are red, yellow or orange-yellow coloring matters and are used as dyes and laxatives.

Anthraquinone is a tricyclic structure in which the quinonoid double bonds have less activity than those in quinone or naphthoquinone. This is perhaps due to their inclusion into the aromatic rings. This results in anthraquinone having weak reducing properties and thus very useful properties for treating some skin conditions. (See anthrarobin).



Anthraquinone

Anthraquinone is readily prepared from anthracene by oxidation, using nitric acid, dichromate with sulfuric acid or air (oxygen) with vanadium oxide as the catalyst.

It occurs as yellow needles which are odorless, only slightly soluble in most solvents and readily sublimed. This compound is very stable and is attacked only with difficulty by nitric acid or other oxidizing agents. Chemically, it resembles the diketones more than the quinones.

Several important dye stuffs are derivatives of anthraquinone (see Table 20). Many of these, such as purpurin and alizarin, possess laxative action also, but are used only as

dyes. Note that the laxative anthraquinones (emodins) have in position three another group such as methyl, carboxyl, or hydroxy methyl (CH_2OH). (See Glycosides, Chapter 24.)

Other polyhydroxy anthraquinone derivatives such as alizarin, Bordeaux, anthracene blue and carminic acid are used as dyes. (See Chapter 21). Of these, carminic acid, because of its presence in cochineal, is used as a coloring material in pharmacy.

TABLE 20. HYDROXYANTHRAQUINONE DYES

NAME	CHEMICAL NAME
Alizarin	1,2-Dihydroxyanthraquinone
Quinizarin	1,4-Dihydroxyanthraquinone
Anthrarufin	1,5-Dihydroxyanthraquinone
Chrysazin	1,8-Dihydroxyanthraquinone
Anthraoflavin	2,6-Dihydroxyanthraquinone
Hystazarin	2,3-Dihydroxyanthraquinone
Anthragallol	1,2,3-Trihydroxyanthraquinone
Purpurin	1,2,4-Trihydroxyanthraquinone
Flavopurpurin	1,2,6-Trihydroxyanthraquinone
Anthrapurpin	1,2,7-Trihydroxyanthraquinone

Carminic Acid. This complex hydroxy-anthraquinone is obtained from Cochineal U.S.P. It is readily extracted with water and may be crystallized as bright red needles. The compound is originally red, but due to the presence of one carboxyl group, forms "lakes" with metals such as tin (cochineal scarlet) and aluminum, producing colors of crimson, scarlet and violet. It is used primarily as a mordant dye for silk and wool.

Cochineal Solution N.F. is essentially an acid solution of carminic-acid-aluminum "lake" and is used to color pharmaceuticals that are acid in reaction. The solution is incompatible with alkali.

Carmine N.F. is essentially the carminic-acid-aluminum "lake" prepared from the coloring principle present in cochineal. It is a red, solid material which has both acid- and base-soluble fractions. As previously stated, Cochineal Solution N.F. contains the acid-soluble portion, whereas **Carmine Solution N.F.** contains the base-soluble fraction.

Emodin. In nature there is found a group

of isomeric hydroxyanthraquinone derivatives that may occur as glycosides or as methyl ethers as well as in the free state. These are all strong cathartics, having a substituent in position three (3), and are known collectively as emodins. They are found in such drugs as aloes, rhubarb, cascara, senna and wild cherry (see Chapter 24).

Purgative action of drugs containing an emodin is thought by some to be due in part to other constituents such as resins. The mechanism¹⁵ of action of the anthraquinone purgatives was determined on frangula-emodin. It was found to decrease the tone of the duodenum, the small intestine and the proximal portion of the colon. The strength, but not the amplitude, of the colonic contractions was increased. This action is like that of acetylcholine and is inhibited by atropine; thus, emodin may exert a parasympathomimetic action. Perhaps it affixes itself to the muscle protein of the intestinal wall. This appears to be the basis for prescribing belladonna with emodin-containing drugs (i.e., aloes) to reduce griping.

Recent work on the estimation of Aloin (U.S.P.) in Aloes (U.S.P.) indicates that the dose of aloin or emodin preparations should be regulated by the quantity of emodin in the original drug. Stone¹⁶ found that the dose of aloin varied 25 per cent in aloes preparations because the amount of aloin in aloes varies from lot to lot.

OFFICIAL OCCURRENCE

U.S.P.

Aloin

Aloes

Cascara Sagrada

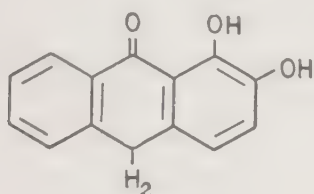
Rhubarb

ANTHRAQUINONE
REDUCTION PRODUCTS

The partially reduced compounds related to anthraquinone are of value in treating certain skin diseases (eczema and psoriasis). All of these have the carbonyl group in position ten (10) reduced to methylene (CH_2).

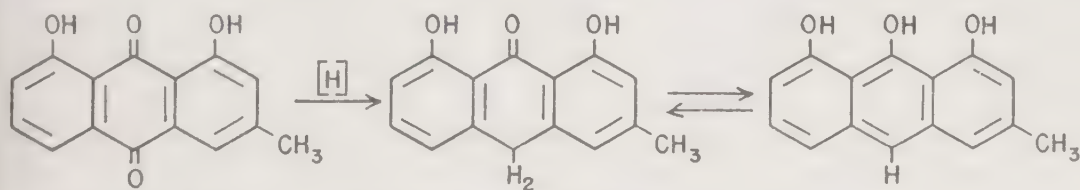
Anthrarobin (Dihydroxyanthranol) is derived from alizarin by reacting it with zinc

and ammonia. It is soluble in chloroform or in ether, and insoluble in water or in acid media. Anthrarobin is a strong reducing agent which readily absorbs oxygen, thereby being converted to blue alizarin. It is, of course, incompatible with oxidizing agents. It has a mode of action similar to that of chrysarobin and is employed in skin disorders as a 10 per cent solution or ointment.



Anthrarobin

Chrysarobin U.S.P. "Chrysarobin is a mixture of neutral principles obtained from Goa Powder." This is a mixture of the reduction products of chrysophanic acid and emodin, obtained by extracting Goa powder with warm benzene or chloroform and evaporating the extract to dryness.



Chrysophanic Acid

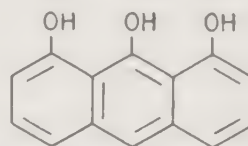
Chrysophanic Acid Anthrone

These reduction products¹⁷ are called anthrones, dianthrones and anthranols, and are commonly referred to as "neutral principles." The complex mixture is soluble in ether, chloroform (1:15) or alcohol (1:400), and is slightly soluble in water.

It is used in ointment form and in collodion in about 5 per cent strength. The mode of action in treating skin diseases is thought to be the removal of oxygen from the surrounding tissue, since the "neutral principles" are very active reducing agents. Various skin conditions, such as eczema, ringworm infections and psoriasis, are treated with this powder.

OFFICIAL OCCURRENCE U.S.P.	PER CENT CHRYSAROBIN
Chrysarobin Ointment	6.0

Dioxyanthranol is a synthetic compound occurring as a yellow crystalline powder. Its



Dioxyanthranol

solubilities and uses are similar to those of chrysarobin. It has several advantages such as that of exact composition, less irritation, effectiveness in low concentration and little discoloration of skin and clothes. Several proprietary preparations of it are available.

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15

Aromatic Acids, Their Salts and Esters

BENZOIC ACID DERIVATIVES

SALICYLIC ACID DERIVATIVES

COMPOUNDS OF TYPE I

THE SALOL PRINCIPLE

COMPOUNDS OF TYPE II

p-HYDROXYBENZOIC ACID DERIVATIVES

p-ALKOXYBENZOIC ACID DERIVATIVES

p-ARYLOXYBENZOIC ACID DERIVATIVES

VANILLIC ACID DERIVATIVES

p-AMINOBENZOIC ACID DERIVATIVES

LOCAL ANESTHETICS

PROPERTIES

MODE OF ACTION

MANDELIC ACID DERIVATIVES

TROPIC ACID DERIVATIVES

DIPHENYLACETIC ACID DERIVATIVES

FLUORENE-9-CARBOXYLIC ACID DERIVATIVES

CHEMICAL CONSTITUTION AND MYDRIASIS

CINNAMIC ACID DERIVATIVES

IDOAROMATIC ACID DERIVATIVES

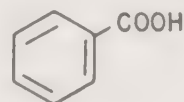
LACTONES

For purposes of this chapter, aromatic acids are considered as those organic molecules containing an aryl group and a carboxyl group. The carboxyl group may or may not be attached to the aryl group. These acids are usually used to form physiologically active esters with alcohols that contribute substantially to their medicinal value. The types of physiologically active compounds found in this group range through analgesics, antispasmodics, local anesthetics, contrast structures and antiseptics.

BENZOIC ACID DERIVATIVES

Benzoic Acid, U.S.P. (Phenylformic Acid). Benzoic acid and its esters occur in nature as constituents in gum benzoin, in Peru and Tolu balsams and in cranberries.

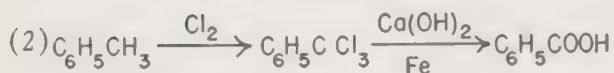
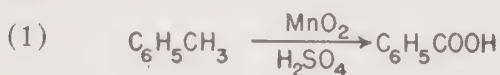
As hippuric acid, it occurs in combination with glycine in the urine of herbivorous animals.



Benzoic Acid

The acid may be obtained by distillation from a natural product, such as benzoin or prepared synthetically by several procedures. For benzoic acid there are a number of syntheses, for example, the Cannizzaro reaction with benzaldehyde, the Friedel-Crafts reaction of phosgene on benzene, the hydrolysis of hippuric acid, the oxidation of benzyl alcohol, the hypohalite oxidation of acetophe-

none, the oxidation of toluene (1), and the chlorination, then hydrolysis, of toluene (2).



Benzoic acid forms white crystals, scales or needles, that are odorless or may have a slight odor of benzoin or benzaldehyde. It sublimes at ordinary temperature and distills with steam. It is slightly soluble in water (0.3 per cent), benzene (1 per cent) and benzin, but it is more soluble in alcohol (30 per cent), chloroform (20 per cent), acetone (30 per cent), ether (30 per cent) and volatile and fixed oils.

All of the reactions characteristic of the carboxyl group are exhibited by benzoic acid. Reactions characteristic of aromatic compounds, as, for instance, nitration, halogenation and sulfonation, take place with benzoic acid. The acid is more strongly acidic (K_a 6.8×10^{-5}) than acetic acid (K_a 1.8×10^{-5}), and most of the common electron-attracting substituents increase the acidity. Solutions containing the ions of iron, silver, lead or mercury form a precipitate of the respective salt with benzoic acid. The iron salt is a reddish-tan or salmon-colored precipitate.

Benzoic acid is used externally as an antiseptic,¹ and is employed in lotions, ointments and mouthwashes. In concentrations over 0.1 per cent it may produce local irritation. It is employed as a food preservative, especially in the form of its salts (i.e. sodium benzoate). Internally, it is irritating to the stomach and therefore, usually is administered in the form of salts. There is thought to be some antirheumatic effect because with its usage, the uric acid content of the urine is increased. As with most aromatic acids, it is detoxified and eliminated, in combination with glycine, as hippuric acid.

OFFICIAL OCCURRENCE	PER CENT BENZOIC ACID
U.S.P.	
Acacia Mucilage	0.2
Aluminum Hydroxide Gel.....	0.5
Aluminum Phosphate Gel	0.5
Camphorated Opium Tincture...	0.4
Starch Glycerite	0.2
Tragacanth Mucilage	0.2
N.F.	
Aromatic Spray	0.3
Benzoic and Salicylic Acid Ointment	12.0
Aminoacetic Acid Elixir.....	0.2
Pectin Paste	0.2
Thin Pectin Paste.....	0.2

Ammonium Benzoate. This salt is prepared by neutralizing ammonium hydroxide with benzoic acid. It occurs as a white, crystalline powder or as fine crystals, and is soluble in water, alcohol or glycerin. The incompatibilities are similar to those of benzoic acid. When warmed or heated in the dry state, it behaves as do all ammonium salts of organic acids, by decomposing with the liberation of ammonia. Aqueous solutions of the compound are alkaline and if made acid, cause the precipitation of benzoic acid.

It is used for the benefits derived from the benzoate ion. The irritant action of benzoic acid on the stomach when it is used internally, is decreased by salt formation, which also decreases the antiseptic action. Ammonium benzoate probably owes its antiseptic activity to the free undissociated benzoic acid present; this, of course, depends on the pH of the medium. The salt is thought to possess some antiseptic and diuretic effects.

The average dose is 1.0 Gm.

Lithium Benzoate N.F. The benzoate of lithium is prepared from lithium carbonate and benzoic acid. It occurs as small, shining, crystalline scales or as a white powder. It is stable in air, has an alkaline, sweetish, cooling taste and is odorless. The salt is soluble in water (1:3) and in alcohol (1:16).

Its chemical properties and uses are the same as those of ammonium benzoate. Lithium and its uses are discussed in a recent book by Rogers.²

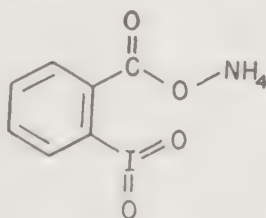
The average dose is 1.0 Gm.

Sodium Benzoate U.S.P. Sodium benzoate is prepared by adding sodium bicarbonate to an aqueous suspension of benzoic acid. The product has a sweet, astringent taste; it is stable in air and is a white, odorless, crystalline substance or a granular powder. It is soluble in water or alcohol.

Sodium benzoate has chemical properties similar to those of all benzoates (i.e. ammonium benzoate). It is used primarily as a preservative in acid media for the antiseptic effect of benzoic acid. The solubilizing property for caffeine is used in the official physical mixtures (q.v.). This salt is used internally as a test for liver function. The benzoate is detoxified by glycine and excreted as hippuric acid, formation of which takes place in the liver, so that the rate at which this material is excreted determines the functional ability of the liver.

OFFICIAL OCCURRENCE	PER CENT SODIUM BENZOATE
U.S.P.	
Caffeine and Sodium Benzoate	50.0
Caffeine and Sodium Benzoate Injection	...
N.F.	
Acacia Syrup	0.1
Caffeine and Sodium Benzoate Tablets	...

Amidoxyl Benzoate (Ammonium *o*-Iodoxybenzoate), $C_6H_4(IO_2)COONH_4$, is an ammonium salt of *o*-iodoxybenzoic acid that contains iodine. The iodine is present in the pentavalent state.

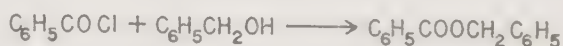


Amidoxyl Benzoate

It occurs as an odorless, white, crystalline powder that possesses a slightly bitter taste. The iodine content is about 43 per cent. The salt is soluble in water and slightly soluble in alcohol. It is used intramuscularly in

about 0.35 Gm. doses as an analgesic and antiarthritic.

Benzyl Benzoate U.S.P. This ester occurs naturally in Peru balsam and in some resins. It is prepared synthetically from benzyl alcohol and benzoic acid by several methods, such as that using benzyl alcohol and benzoyl chloride.



The ester is a clear, oily, colorless liquid, having a faint aromatic odor and a sharp, burning taste. The liquid is insoluble in glycerin and water, but is miscible in all proportions with chloroform, alcohol or ether. It congeals at about 18° to 20° C.

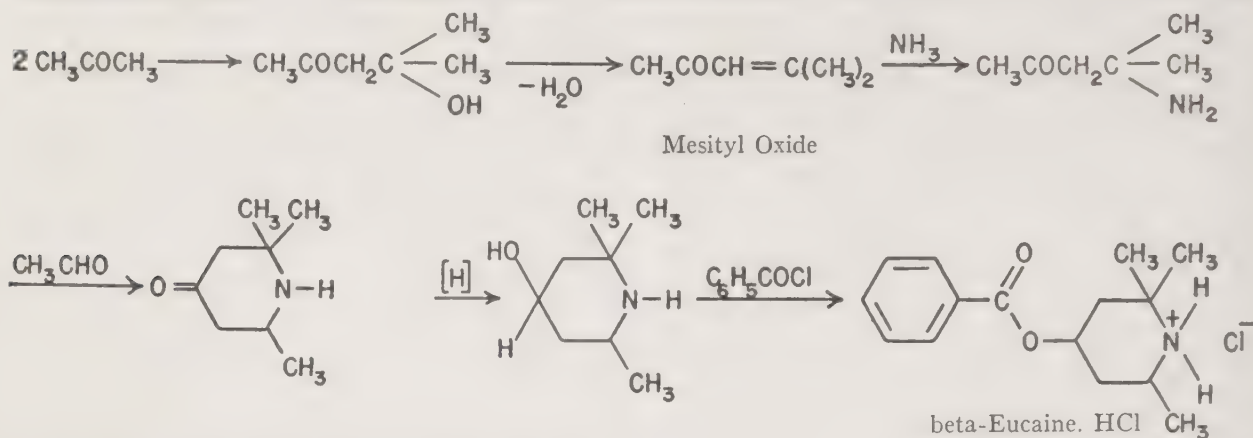
Benzyl benzoate is neutral to litmus and with potassium hydroxide, is readily saponified.

It was first introduced into medicine about twenty years ago as an antispasmodic (q.v.) because of the benzyl group, but in 1937³ it was found to be an effectual parasiticide of especial value for the treatment of scabies by local application. For scabies, a 25 per cent emulsion is usually used. Due to some local anesthetic effect, there is instantaneous relief from itching. A single treatment often produces a complete cure.⁴ Other advantages are absence of odor, freedom from staining of clothes and no skin irritation.

OFFICIAL OCCURRENCE	PER CENT BENZYL BENZOATE
U.S.P.	
Benzyl Benzoate Lotion.....	25
Saponated Benzyl Benzoate..	100

β-Naphthol Benzoate (Benzonaphthol) is a solid ester prepared synthetically from β-naphthol and benzoic acid. It occurs as tasteless, colorless, crystals that are insoluble in water but soluble in organic solvents.

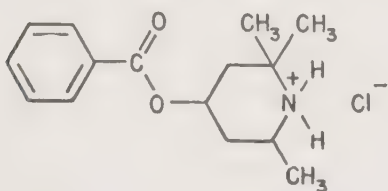
Internally, it has weak antiseptic properties, which have led to its use as an intestinal antiseptic in the treatment of diarrhea and dysentery, and it is used as a vermifuge. Externally, in the form of ointments (3 to 10



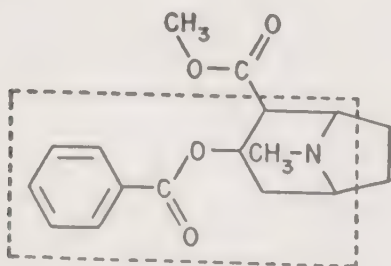
per cent), it is used as a parasiticide, but is less effective against scabies than is benzyl benzoate.

Guaiacol Benzoate (Benzosol) is a "full salol" or "true salol" (q.v.) combining the properties of guaiacol (a phenol) and benzoic acid. It is prepared synthetically and occurs as a white powder, insoluble in water and soluble in the usual organic solvents. It was once used internally as an antiseptic in the digestive tract, but has been replaced by better products.

Eucaine Hydrochloride N.F. (Betaeucaine Hydrochloride, Betachine, Benzamide).



Eucaine was one of the first synthetic local anesthetics developed by Harries⁵ soon after the elucidation of the cocaine molecule. On examination of the cocaine molecule, that portion related to eucaine is readily observed.



The part enclosed by a dotted line is essentially the basis of eucaine. The development of this local anesthetic confirmed in part the essential portion of the cocaine molecule responsible for local anesthetic action.

It is, comparatively, a cheap compound since it is synthesized from readily available materials. For the details of this synthesis see the equations at the top of the page.

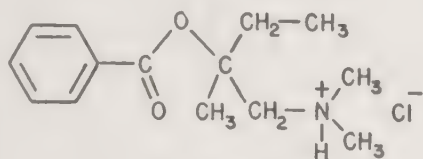
The hydrochloride of eucaine is an odorless, white, crystalline powder, stable in air. It is affected by light and soluble in water, alcohol and chloroform, but insoluble in ether. Aqueous solutions of the hydrochloride are stable and may be sterilized by boiling, but the presence of alkalis or carbonates will decompose it. The lactate salt has also been prepared and used.

It has the advantage over cocaine of not being habit forming, not being a mydriatic and not being a vasoconstrictor, although it does come under the Harrison narcotic act. The action is a little slower than that of cocaine, but it is less irritating. Since it is more toxic than procaine, procaine has become the drug of choice. Eucaine hydrochloride is applied in 1 to 5 per cent solutions.

A full discussion of compounds possessing a local anesthetic effect is given following ethyl aminobenzoate.

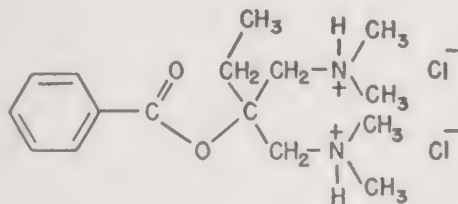
Amylocaine (Amylocaine Hydrochloride, Stovaine). Amylocaine was one of the early

local anesthetics (see ethyl aminobenzoate), synthesized after the introduction of cocaine and based on information obtained from the cocaine molecule. It is an ester of benzoic acid and 1,1-ethylmethyl-2-dimethylaminoethanol. The hydrochloride is a white, crystalline powder, insoluble in ether, but soluble in water or alcohol. It is inefficient for surface anesthesia, but is effective when injected. A 1 per cent solution is usually used for local anesthesia.



Amylocaine

Amydricaine Hydrochloride N.N.R. (Alypin Hydrochloride). Alypin is essentially an ester of benzoic acid and the dialkylamine alkyl alcohol [1 bis-(dimethylaminoethyl)-1-propanol]. It is readily synthesized from benzoyl chloride and the dialkylaminoalkyl alcohol (See procaine). It is the stovaine molecule with an added dimethylamino group (q.v.).



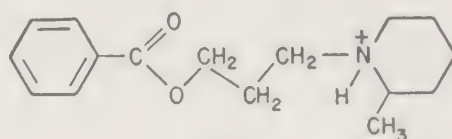
Amydricaine Hydrochloride

In the form of the hydrochloride it occurs as an odorless, white, crystalline, hygroscopic powder. It is insoluble in ether and soluble in alcohol, chloroform or water. It is unstable in the presence of heat when in aqueous solution, but may be boiled for five minutes.

It is used as a substitute for cocaine, to which it is about equal in local anesthetic action (See ethyl aminobenzoate). However, it does not have any mydriatic action. The toxicity is greater than that of cocaine

and it relaxes rather than constricts blood vessels. As a local anesthetic, it is relatively ineffective when applied locally to unbroken skin or mucous membranes, but is satisfactory when injected. Freshly prepared, sterile solutions of 2 to 5 per cent are employed.

Metycaine Hydrochloride N.N.R. (Neothesine). Metycaine is an ester of benzoic acid with the basic alcohol γ -(2-methylpiperidino) propanol. Since there is an asymmetric carbon atom present, the racemic mixture of the hydrochlorides is used. The solubility is similar to that of the hydrochlorides of other basic esters, and it is used as a local anesthetic by subcutaneous injection or topical application to mucous membranes. It has about the same toxicity as procaine by subcutaneous injection and is about one-third as toxic as cocaine. Intravenously, it is three times as toxic as procaine. In the eye, metycaine is used in 2 per cent solutions; in the nose and throat, 2 to 10 per cent solutions; in the urethra, 1 to 4 per cent solutions, and in subcutaneous injections, 0.5 to 1 per cent solutions. Metycaine has been used successfully in caudal anesthesia.

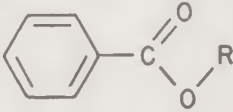
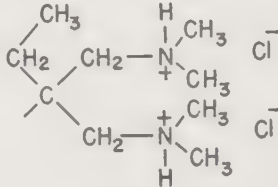
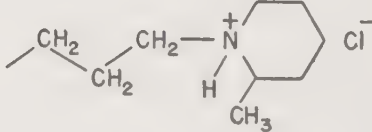
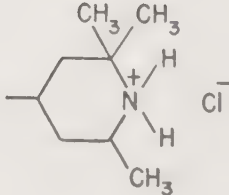
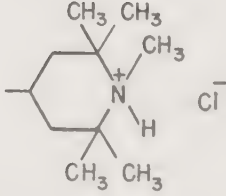
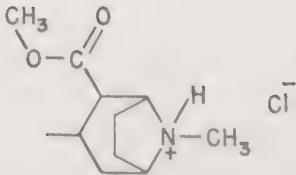


Metycaine

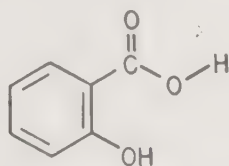
Table 21 (page 188) shows some local anesthetics that are esters of benzoic acid and an amino-alcohol.

Salicylic Acid U.S.P. (*o*-Hydroxybenzoic Acid). This acid has been known for over one hundred years, having been discovered in 1839. It is found free in nature and in the form of salts and esters. A very common ester is methyl salicylate (oil of wintergreen). Salicylic acid may be obtained from oil of wintergreen by saponification with sodium hydroxide and then neutralization with hydrochloric acid. This is referred to as

TABLE 21. LOCAL ANESTHETICS THAT ARE ESTERS OF BENZOIC ACID AND AN AMINO-ALCOHOL

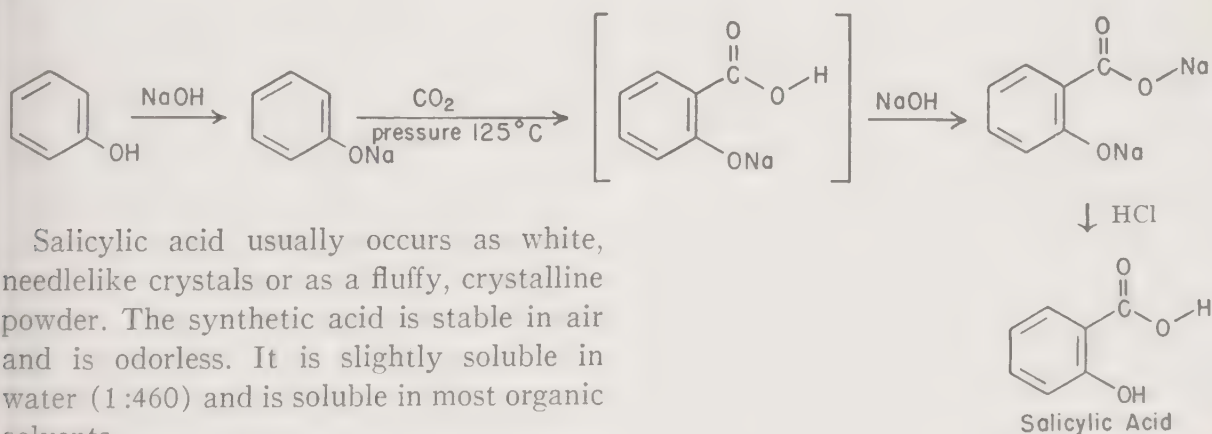
NAME	FORMULA OF R
Amylocaine Hydrochloride	
Amydricaine Hydrochloride	
Metycaine Hydrochloride	
Eucaïne Hydrochloride	
α-Eucaïne Hydrochloride	
Cocaine Hydrochloride	

"natural salicylic acid" and is used to prepare salts which are preferred by some. The natural acid is usually tinted pink or yellow and has a faint wintergreenlike odor. At one time it was believed that the synthetic salicylic acid was contaminated with some cresotinic acid [$C_6H_3.CH_3(OH)(COOH)$] and was thus more toxic, its salts less desirable. It has since been shown, not only that cresotinic acid is absent, but also that cresotinic acid is nontoxic.



Salicylic Acid

In 1859, Kolbe introduced a synthetic method for its preparation and, with slight changes, this is still used. Sodium phenolate is prepared and saturated under pressure with carbon dioxide; the resulting product then is acidified and salicylic acid is isolated.



Salicylic acid usually occurs as white, needlelike crystals or as a fluffy, crystalline powder. The synthetic acid is stable in air and is odorless. It is slightly soluble in water (1:460) and is soluble in most organic solvents.

The chemical properties of this acid are due to the phenolic hydroxyl group (see Chap. 14) and to the carboxyl group. Since it is also a phenol, it responds with the reactions of phenols, such as those of producing a violet color with ferric salts, halogenation, nitration and oxidation. Oxidizing agents form colored compounds, perhaps of a quinoid⁶ type, and destroy the molecule. The colored compounds produced on stand-

ing in alkaline solution are due to quinhydrone formation. For examples of quinhydrone formation see the equations at the top of page 190.

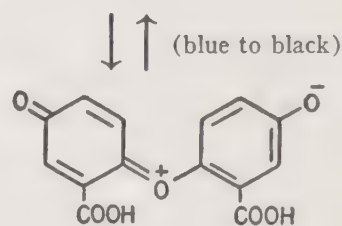
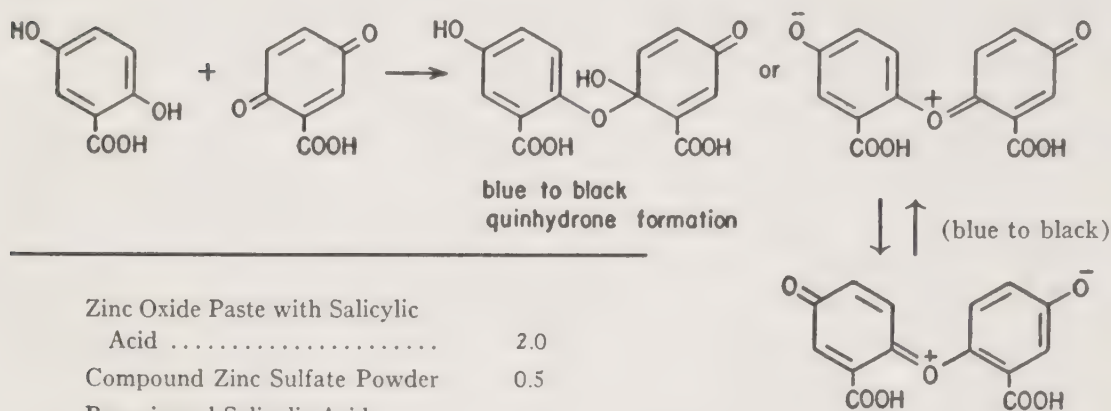
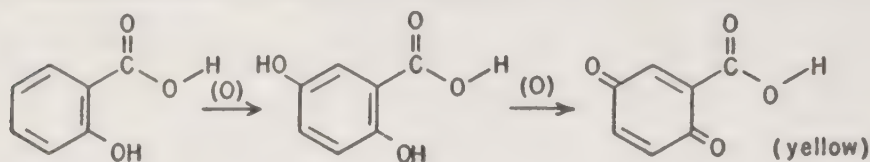
Insoluble salts are formed with ions of the heavy metals such as silver, mercury, lead, bismuth and zinc. Reducing agents break down salicylic acid to pimelic acid. Boric acid and salicylic acid combine to form borosalicylic acid.

Salicylic acid has strong antiseptic and germicidal properties, due to the fact that it is a carboxylated phenol. The presence of the carboxyl group appears to enhance the antiseptic property and to decrease the destructive, escharotic effect. It is used as a preservative in foods and pharmaceuticals and externally as a mild escharotic and antiseptic in ointments and solutions. Internally, it is seldom administered as the free acid, but is taken in the form of its salts for the effects of the salicylate portion. In the circulatory system, it exists as sodium salicylate and exerts a marked antipyretic and

analgesic effect. In salt form, it has extensive use in acute articular rheumatism and rheumatic fever. The 1949 N.N.R. states that all the clinical needs of salicylates are met by the official forms.

The average dose is 1.0 Gm.

OFFICIAL OCCURRENCE	PER CENT SALICYLIC ACID
N.F.	
Salicylic Collodion	10.0



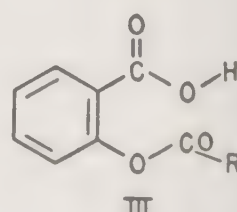
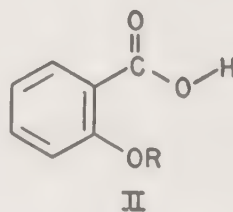
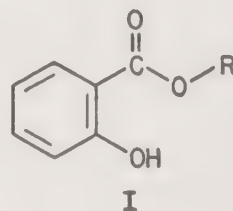
SALICYLIC ACID DERIVATIVES

The physiologic activity of salicylic acid and its derivatives is difficult to explain when it is observed that phenol does not possess any antipyretic or analgesic action and that benzoic acid is quite weak in this action. Usually, the introduction of a hydroxyl group will weaken any physiologic action that a compound exhibits. This appears untrue when salicylic acid (*o*-hydroxybenzoic) is derived from benzoic acid, but does hold for *m*- and *p*-hydroxybenzoic acids, which are devoid of any analgesic, antipyretic or antirheumatic action. Also, the introduction of a carboxyl group will decrease the activity of a structure; a case in point is that of phthalic acid, which is physiologically inactive. When the carboxyl group is separated from the aromatic ring, as in phenylacetic acid or in cinnamic acid, all trace of the original physiologic action of benzoic acid is lost.

Now, if one considers the original compound, phenol, and introduces a carboxyl group, the corrosive effect, escharotic action, antiseptic property and reactivity toward proteins is decreased. In the case of the *m*-

and *p*-hydroxybenzoic acids, these properties are practically lost. Salicylic acid (*o*-carboxyphenol) has the physiologic properties of both phenol and benzoic acid, plus an antirheumatic action.

The derivatives of salicylic acid are of two kinds:



Formula I represents those which are formed by esterifying the carboxyl group. Formulas II and III represent those which are derived by substitution on the hydroxyl group of salicylic acid. The derivatives of salicylic acid were introduced to prevent the gastric symp-

toms and the undesirable taste inherent in the common salts of salicylic acid. Hydrolysis of type III takes place to the greater extent in the intestine and most of type I compounds are absorbed into the blood stream. (See Aspirin). All of these derivatives retain some properties of the original phenol, benzoic acid or salicylic acid, and differ only in intensity of action.

COMPOUNDS OF TYPE I

Ammonium Salicylate N.F. is prepared by evaporating to dryness a slightly acid solution composed of a mixture of ammonium hydroxide and salicylic acid.

It occurs as colorless, lustrous plates or monoclinic prisms, or as a white, crystalline powder. The compound is odorless and has at first a slightly saline, bitter taste, with a sweetish aftertaste. The salt is stable in dry air. It is soluble in water (1:1) and in alcohol (1:3).

Ammonium salicylate has the characteristic of all ammonium salts of organic acids (See ammonium benzoate) and of salicylates.

The salt is used primarily for the internal administration of salicylate.

The average dose is 1.0 Gm.

Lithium Salicylate N.F. By heating a mixture of salicylic acid (2 moles) and lithium carbonate (1 mole) in water, lithium salicylate is prepared. It usually is found as a white or grayish-white powder; it is odorless or has a faint, characteristic odor and has a sweetish taste. The compound is deliquescent and very soluble in water and alcohol.

The reactions are those typical of salicylates (See sodium salicylate and salicylic acid).

The average dose is 1.0 Gm.

Due to the fact that lithium was once thought to be beneficial in certain types of rheumatism, this salt was once looked upon as being especially effective.

Sodium Salicylate U.S.P. may be prepared by the reaction, in aqueous solution,

between one mole each of salicylic acid and sodium bicarbonate; upon evaporating to dryness, the white salt is obtained.

Generally, the salt has a pinkish tinge or is a white, microcrystalline powder. It is odorless or has a faint, characteristic odor and it has a sweet, saline taste. It is affected by light. The compound is soluble in water (1:1), alcohol (1:10) and glycerin (1:4).

In solution, particularly in the presence of sodium bicarbonate, the salt will darken on standing (See salicylic acid). This darkening may be lessened by the addition of sodium sulfite or sodium bisulfite.⁶ Sodium salicylate forms a eutectic mixture with antipyrine and produces a violet coloration with iron or its salts. Solutions of the compound must be neutral or slightly basic, to prevent precipitation of free salicylic acid. The U.S.P. salt, however, forms neutral or acid solutions.

This salt is the one of choice for salicylate medication and usually is administered with sodium bicarbonate to lessen gastric distress, or it is administered in enteric-coated tablets. The use of sodium bicarbonate⁷ is ill-advised since it has been shown to decrease the plasma levels of salicylate and to increase the excretion of free salicylate in the urine.

The average dose is 0.3 Gm.

OFFICIAL OCCURRENCE	PER CENT SODIUM SALICYLATE
N.F.	
Sodium Salicylate Ampuls..	..
Compound Sodium Salicylate and Gelsemium Elixir...	8.0
Sodium Salicylate and Iodide Ampuls	..
Sodium Salicylate and Iodide with Colchicine Ampuls	..
Sodium Salicylate Elixir..	8.5
Caffeine and Sodium Salicylate	50.0
Theobromine and Sodium Salicylate	50.0

Strontium Salicylate N.F. Preparation of strontium salicylate may be carried out by adding strontium carbonate (1 mole) to a suspension of salicylic acid (2 moles) in hot water. The hot mixture, after effervescence

ceases, is filtered and evaporated to dryness. The compound is a white, odorless, crystalline powder, possessing a somewhat sweet, saline taste. It is soluble in water (1:19) and alcohol (1:61).

Strontium salicylate is chemically similar to the other salicylates and is used for the same conditions.

The average dose is 1.0 Gm.

Bismuth Subsaliolate U.S.P. This material is a basic salt of varying composition, prepared from solutions of sodium salicylate and bismuth nitrate. The bismuth is attached not only to the carboxyl group of salicylic acid, but also to the phenolic hydroxyl group.

It occurs as a nearly white, fine, crystalline or amorphous powder that is stable in air but affected by light. The product is insoluble in water.

Bismuth subsaliolate is used for the protective benefits of bismuth in gastro-enteritis and for the antiseptic effect of salicylic acid, which is slowly formed as the material is hydrolyzed. Bismuth, in the form of insoluble organic compounds, is useful in the treatment of syphilis (see Chapter 19). The subsaliolate, in an oily suspension, is administered intramuscularly as an anti-syphilitic.

The average dose is 1 Gm. given orally or 0.1 Gm. intramuscularly.

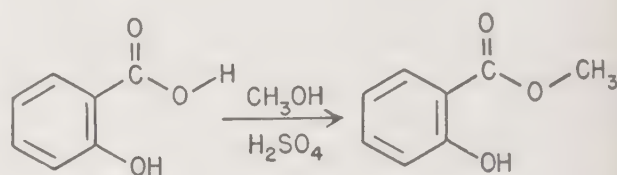
The alkyl and aryl esters of salicylic acid (Type I) are used externally primarily as counterirritants, where most of them are well absorbed through the skin. This type of compound is of little value as an analgesic.

A few inorganic salicylates are used internally when the effect of the salicylate ion is intended. These compounds vary in their irritation of the stomach. To prevent the development of pink or red coloration in the product, contact with iron should be avoided in the manufacture.

Methyl Salicylate (Wintergreen Oil, Sweet Birch Oil, Betula Oil, Gaultheria Oil) U.S.P. (Oil of Teaberry, Artificial Oil

of Wintergreen, Synthetic Oil of Wintergreen). "Methyl Salicylate is produced synthetically or is obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* Linné (Fam. *Ericaceae*) or from the bark of *Betula lenta* Linné (Fam. *Betulaceae*)."

It is prepared synthetically through the esterification of salicylic acid with methyl alcohol in the presence of sulfuric acid.



Methyl salicylate is a colorless, yellowish or reddish, fragrant, oily liquid, slightly soluble in water and miscible with alcohol. It is usually labeled to indicate whether it was prepared synthetically or distilled from natural sources.

Only the carboxyl group of salicylic acid has reacted with methyl alcohol. The hydroxyl group, therefore, reacts with ferric chloride T.S. to produce a violet color. It is readily saponified by alkalies and reacts like the other salicylates.

It is used most often as a flavoring agent and in external medication as a rubefacient in liniments. In water and hydro-alcoholic solutions, it is rapidly absorbed, thus penetrating deeply into the tissue and exerting also a systemic action. There is some use made of it internally for salicylate therapy.

The average dose is 1.0 cc.

OFFICIAL OCCURRENCE	PER CENT METHYL SALICYLATE
U.S.P.	
Cod Liver Oil Emulsion...	0.4
Aromatic Cascara Sagrada Fluidextract	0.01
Compound Sarsaparilla Syrup	0.02
N.F.	
Compound Menthol Spray	0.5
Compound Menthol Ointment	10.0
Alkaline Aromatic Solution	0.05
N.F. Antiseptic Solution..	0.02
Aromatic Spray	0.5

Ephedrine Sulfate Jelly...	0.01
Kaolin Cataplasm	0.2
N.F. Dentifrice	0.8

Mesotan (Salmester, Methoxymethyl Salicylate). Mesotan may be considered as related to methyl salicylate. One hydrogen of the methyl group is replaced by a methoxy group ($\text{CH}_3\text{O}-$). It is synthesized from monochlorodimethylether and sodium salicylate. Mesotan is slightly soluble in water, readily soluble in the usual organic solvents and miscible with fixed oils. It is a clear, yellowish, faintly aromatic liquid. The liquid should be stored in a cool place and in dry, well-stoppered bottles since it is decomposed easily by heat and moisture.

Mesotan, in aqueous solution, gives a violet color with ferric chloride because the hydroxyl group of salicylic acid is uncombined. The compound, after heating or exposure to moisture, releases formaldehyde as a decomposition product and this may be detected by qualitative tests. Upon heating above 100°C ., salicylic acid and methyl alcohol are also formed. Sulfuric acid produces a red color with mesotan.

Mesotan is applied to the skin by first diluting it with 1 to 4 parts of olive oil or cottonseed oil and painting over the area. Care must be exercised in its use in that no rubbing is permissible; only slight covering should be used and frequent change of site of application is advisable. It is obtainable in bulk liquid form.

It is a good counterirritant and is used externally in rheumatic conditions although some is absorbed through the skin. The action is mainly local in relieving swelling and pain. It is not satisfactory for internal use.

Ethyl Salicylate (Sal-Ethyl). Ethyl salicylate is the salicylic acid ester of ethyl alcohol, prepared in an analogous manner to the preparation of methyl salicylate, ethyl alcohol replacing methyl alcohol.

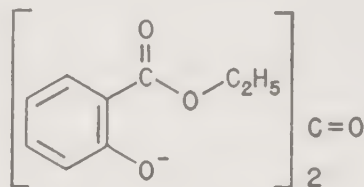
It is a transparent, colorless, volatile liquid, possessing a pleasant, characteristic odor and taste. Ethyl salicylate is insoluble

in water, but is soluble in alcohol.

It is said to be less toxic and less irritant than methyl salicylate and not as readily absorbed through the skin. This ester has the same action and uses as methyl salicylate.

The average dose is 0.5 cc.

Sal-ethyl Carbonate. Sal-ethyl carbonate is an ester type compound of ethyl salicylate and carbonic acid. It is the carbonic acid ester salicylate and thus it may be classified as a type I or type II compound.



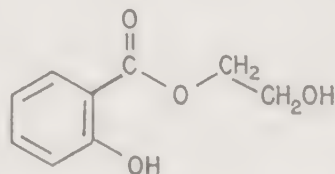
It occurs as white crystals, insoluble in water and in diluted hydrochloric acid, slightly soluble in alcohol or ether and readily soluble in chloroform or acetone. The insolubility tends to prevent gastric irritation and makes it tasteless.

When gently warmed with alcoholic potassium hydroxide, it forms ethyl salicylate and potassium carbonate, the latter precipitating out. By boiling an aqueous solution of sal-ethyl carbonate for about thirty minutes and then acidifying, salicylic acid may be extracted with ether.

In action and uses it resembles Aspirin (Type I) and gives the antipyretic and analgesic effects of the salicylates. The pharmaceutical forms are powder, tablet and a tablet containing aminopyrine.

The average dose is 1.0 Gm.

Spirosal (Monoglycolsalicylate, Glysal). Spirosal is the salicylic acid ester of ethylene glycol.



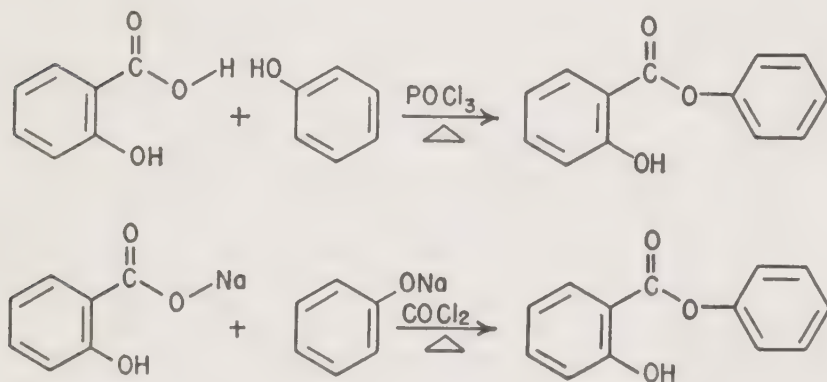
Spirosal is an almost odorless and colorless oily liquid. It is slightly soluble in water

(1:110), easily soluble in olive oil (1:8) and readily soluble in alcohol, ether, chloroform or benzene. In aqueous solution, it is quickly hydrolyzed and will give a violet color with ferric chloride

Salicylic acid can be extracted with ether from the acidified solution after alkaline saponification. When sulfuric acid is added to spirosal, a light yellow color is produced.

Spirosal is supplied in liquid form and is used either undiluted, mixed with from 2 to 3 parts of alcohol, in a mixture with olive oil (1:8) or in ointments with equal parts by weight of petrolatum or lard. The action and use are those characteristic of methyl salicylate, but only about one-fifth to one-sixth of the amount applied to the skin is absorbed. This ester, like mesotan, does irritate.

Phenyl Salicylate (Salol) N.F. Salol, the phenyl ester of salicylic acid, usually is prepared by one of two methods:



Phenyl salicylate is a white, crystalline powder with a characteristic taste and a faint, aromatic odor; it is insoluble in water (1:6700), soluble in alcohol (1:6), ether, chloroform or fixed and volatile oils.

Ferric chloride added to an alcoholic solution produces a violet color, but does not in an aqueous solution. Bromine, by substitution on the phenyl group, produces a precipitate, and nitrous acid in a salol solution causes the mixture to darken.

The formation of damp or eutectic mixtures is readily completed with many organic materials such as thymol, menthol, camphor, chloral hydrate and phenol.

It is insoluble in the gastric juice, but is slowly hydrolyzed in the intestine into phenol and salicylic acid. Because of this fact, it has some use as an enteric coating¹³ for tablets and capsules.

Hydrolysis can be demonstrated by heating it in weak, aqueous alkali for a few minutes, after which, by acidifying the solution, salicylic acid is precipitated and the odor of phenol is noted.

A considerable amount is excreted unchanged in the feces. Because of slow saponification, it is a poor intestinal antiseptic, as the phenol formed is absorbed just as fast as it is liberated, thus preventing an effective concentration to develop. Its usefulness as an intestinal antiseptic, therefore, is questionable. Perhaps a small amount is absorbed into the blood stream.

The average dose is 0.325 Gm.

OFFICIAL OCCURRENCE

N.F.

N.F. Sun Cream

PER CENT SALOL

5.0

THE SALOL PRINCIPLE

Nencki¹⁴ introduced salol in 1886 and by so doing presented to the science of therapy the "Salol Principle." In the case of salol, two toxic substances (phenol and salicylic acid) were combined into an ester which, when taken internally, will slowly hydrolyze in the intestine to give the antiseptic action of its components (q.v.). This type of ester is referred to as a "Full Salol" or "True

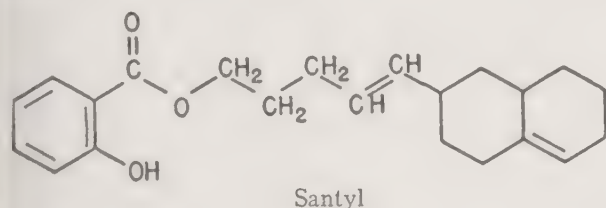
Salol" when both components of the ester are active compounds. Examples are guaiacol benzoate, β -naphthol benzoate, Santyl, and Salol.

This "Salol Principle" can be applied to esters of which only the alcohol or acid is the toxic, active or corrosive portion and this type is called a "Partial Salol."

Examples of a "Partial Salol" containing an active acid are ethyl salicylate, methyl salicylate, mesotan and spirosal. Examples of a "Partial Salol" containing an active phenol are creosote carbonate, thymol carbonate and guaiacol carbonate (see Phenols Chapter 13).

Although a host of the "salol" type compounds have been prepared and used to some extent, none have become very valuable in therapeutics and all are surpassed by other agents.

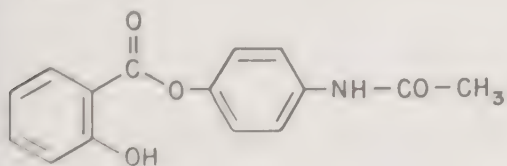
Santyl (Santalyl Salicylate) is the ester of the alcohol β -santalol and salicylic acid, prepared by heating sandalwood oil and the acid.



It is a yellowish oil, insoluble in water, but soluble in alcohol (1:10). In the alkaline medium of the intestines it is hydrolyzed into salicylic acid and the alcohol, β -santalol, but passes through the stomach unchanged (a full or true salol). The ester has the same action as sandalwood oil. However, it is less irritating to the gastro-intestinal tract, the kidneys and the urinary passage. It is claimed to be of use in gonorrheal urethritis.

The average dose is 1.5 cc.

Phenetsal (Salophen, *p*-Acetaminophenyl Salicylate).



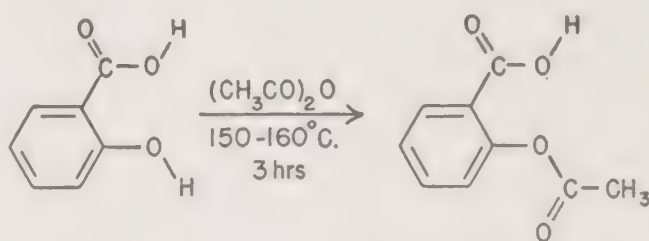
Phenetsal occurs as an odorless, tasteless, fine, white, crystalline powder which is soluble in aqueous alkali, alcohol and most organic solvents, but insoluble in water. It is hydrolyzed in warm, aqueous, alkali solution and there gives the characteristic color reaction of phenols with ferric chloride, although salophen is stable in simple water solution and does not react with ferric chloride.

This ester is a "True Salol" and was prepared for use as a substitute for salol, in hopes that it would be less toxic. It is stable in the stomach and is hydrolyzed in the intestine into salicylic acid and *p*-aminophenol. *p*-Aminophenol is reported to be less toxic than phenol, but is related to the phenetidins and aniline. Many compounds of this type do show deleterious effects on the blood and heart.

It is used as an analgesic, antirheumatic and antipyretic. In a 10 per cent ointment it is used in psoriasis and itching skin diseases. The average dose is 0.5 Gm.

COMPOUNDS OF TYPE II

Acetylsalicylic Acid (Aspirin) U.S.P. (Acetosol, Empirin, Helicon, Salacatin, Salstin). Acetylsalicylic acid was introduced into pharmacy by Dreser in 1899. It is prepared by treating salicylic acid, which was first prepared by Kolbe in 1874, with acetic anhydride.



The hydrogen atom of the hydroxyl group in salicylic acid has been replaced by the acetyl group (CH_3CO); this may also be accomplished by using acetyl chloride with salicylic acid or ketene with salicylic acid.

Aspirin is a not-too-stable, white, crystalline compound which is slightly soluble in

water (1:300) and soluble in alcohol (1:5). Also, it dissolves easily in glycerin or chloroform. Aqueous solubility may be increased by using acetates or citrates of alkali metals,⁹ although these are said to slowly decompose it.

It is stable in dry air, but in the presence of moisture, it slowly hydrolyzes into acetic and salicylic acids. Salicylic acid will crystallize out when an aqueous solution of aspirin and sodium hydroxide is boiled and then acidified.

Aspirin itself is sufficiently acid to produce effervescence with carbonates and, in the presence of iodides, to cause the slow liberation of iodine. In the presence of alkaline hydroxides and carbonates it decomposes, although it does form salts with alkaline metals and alkaline earth metals. The presence of salicylic acid, formed upon hydrolysis, may be confirmed by the formation of a violet color upon the addition of ferric chloride solution.

Acetylsalicylic acid is not hydrolyzed appreciably on contact with weakly acid digestive fluids of the stomach, but on passage into the intestine, is subjected to some hydrolysis. However, most of it is absorbed unchanged. It always should be employed in the dry state, as in tablets, powders or capsules, and never in aqueous solution, because of instability.¹⁰ However, solutions made with alcohol or glycerin do not decompose as quickly. Some studies have indicated that sucrose tends to inhibit hydrolysis.⁹ Acetylsalicylic acid lends itself readily to combination with many other substances but tends to soften and become damp with methenamine, aminopyrine, salol, antipyrine, phenol or acetanilid.

Aspirin is one of the most widely used compounds in therapy and until recently, was not associated with untoward effects. Allergic reactions¹¹ to aspirin now are observed commonly. Asthma and urticaria are the most common manifestations and, when they occur, are extremely acute in nature and difficult to relieve.

Aspirin, methyl salicylate and salicylic acid have been shown to produce a hypoprothrombinemia in animals and man. The effective dose of salicylates (aspirin), is 25 to 100 times that of Dicumarol, and the change in plasma prothrombin is readily prevented by small doses of vitamin K. Link and his associates observed that the only compounds that show anticoagulant action were those which theoretically might yield an *o*-hydroxybenzoic acid (salicylic acid) derivative on degradation. Benzoic acid and *m*- or *p*-hydroxybenzoic acid have no effect on prothrombin time. Due to these findings, tablets of aspirin containing vitamin K have been introduced.

Aspirin is used as an antipyretic, analgesic and antirheumatic, usually in powder, capsule or tablet form. There is some anesthetic action when applied locally, especially in powder form in tonsillitis or pharyngitis, and in ointment form for certain skin itching and skin diseases. In the usual dose, 52 to 75 per cent is excreted in the urine, in various forms, in a period of 15 to 30 hours. The simultaneous administration of sodium bicarbonate increases the absorption rate as well as the rate of elimination. It is believed that analgesia is due to the unhydrolyzed acetylsalicylic acid molecule.¹²

The average dose is 0.325 Gm.

OFFICIAL OCCURRENCE N.F.

PER CENT ASPIRIN

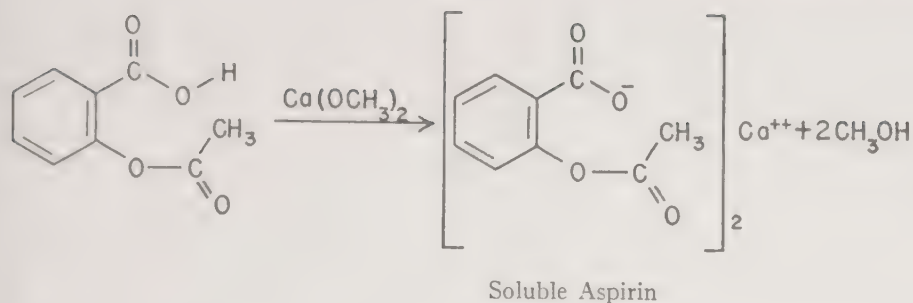
Compound Acetylsalicylic Acid Paste	25.0
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Soluble Aspirin (Calcium Acetylsalicylate, Kalmapyrin, Tylcalcin, Kalsetal). This compound is prepared by treating acetylsalicylic acid with calcium ethoxide or methoxide in alcohol or acetone solution.

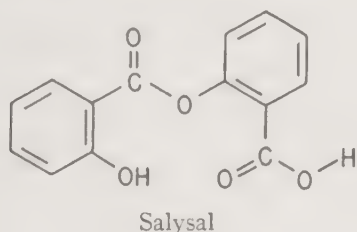
It is readily soluble in water (1:5) and is a crystalline, white powder. It is more stable in solution than is aspirin, and is used for the same conditions.

Lithium acetylsalicylate (litmopyrine, hydropyrine, tyllithin) is another soluble form.

The average dose is 1.0 Gm.



Salysal (Diplosal, Salicylosalicylic Acid). Salysal is the salicylic ester of salicylic acid, prepared by condensing two moles of salicylic acid, using thionyl chloride as the condensing agent.



Salysal is an odorless, tasteless, white, stable, crystalline powder. It is soluble in alcohol, ether or solutions of alkalis; slightly soluble in benzene and insoluble in water or dilute acids. A water solution shows no violet color with ferric chloride solution.

It shows a resistance to acid hydrolysis and is, therefore, less disturbing to the stomach, but is slowly hydrolyzed in the alkaline medium of the intestines. Local irritation and disagreeable taste are thus reduced. Therapeutic use is more like that of sodium salicylate and activity is said to be twice as great.

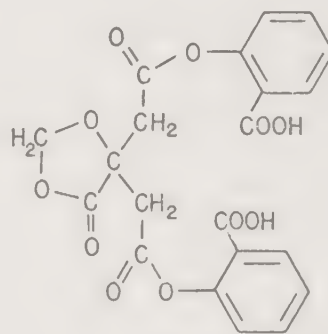
Salysal is available in the powder form and in tablets.

The average dose is 0.325 Gm.

Novaspirin (Methylene-citrylsalicylic Acid, Salicitrin) is a compound of anhydromethylenecitric acid and salicylic acid. Novaspirin is a citric acid derivative of aspirin in which the carboxyl groups of citric acid are attached to two salicylic acid molecules and one oxymethylene group.

Novaspirin is a grayish-white, odorless,

crystalline powder, soluble in alcohol, insoluble in water and slightly soluble in ether or chloroform. It is prepared from salicylic acid and the dichloride of anhydromethylene-citric acid. Novaspirin has chemical properties similar to aspirin, such as those of being easily decomposed by moisture and hydrolyzed with alkalis to give the alkali salicylate and citrate. It is more stable than aspirin in that an aqueous solution prepared without heat does not produce a violet color with ferric chloride solution. It is used as an analgesic and is available in powder and tablets.



Novaspirin

The average dose is 1.0 Gm.

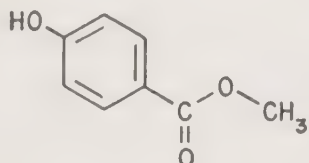
Diaspirin (Succinyl Salicylate). Diaspirin is synthesized from the dicarboxylic succinic acid in the form of succinyl chloride with two moles of salicylic acid.

***p*-Aminosalicylic acid (PAS)** is a well-defined, synthetic, organic compound that has been known for many years and may be prepared by the reduction of *p*-nitrosalicylic acid, using sodium sulfide.¹⁵ Yields of 90 per cent are obtained.

Recent studies¹⁶ indicate that PAS is antagonistic to tubercle bacilli. It is only moderately toxic and may be taken orally.

p-HYDROXYBENZOIC ACID DERIVATIVES

Methylparaben (Methyl Parahydroxybenzoate) U.S.P. (Methylben).



p-Hydroxybenzoic acid may be prepared by the same procedure used for salicylic acid, except that a temperature of about 200° C. is necessary when the carbon dioxide reacts with the sodium phenolate. The free acid possesses only slight antiseptic action, but when esterified (for example with the alcohols methyl, ethyl, propyl or butyl) the resulting compound is very active. Methyl *p*-hydroxybenzoate occurs as small, white crystals or as a crystalline powder which has a slightly burning taste and a faint, characteristic odor or none at all. It is soluble in water (1:400), alcohol (1:2.3) and ether (1:8) and slightly soluble in benzene and in carbon tetrachloride.

The *p*-hydroxybenzoic acid esters are less toxic than those of salicylic or benzoic acid and increase in toxicity as the molecular weight increases. The preservative effect of these esters also increases with the molecular weight; the methyl ester is more effective against molds and the propyl ester more effective against yeasts. The ester grouping apparently behaves like an alkyl group (see hexylresorcinol) in its effect on the antiseptic action. The two esters, methyl and propyl, are pro-oxidants. Oil solubility increases along with the size of the ester group, thus making the propyl ester better than the methyl for oils and fats. The ester may be used to preserve almost any pharmaceutical.¹⁶

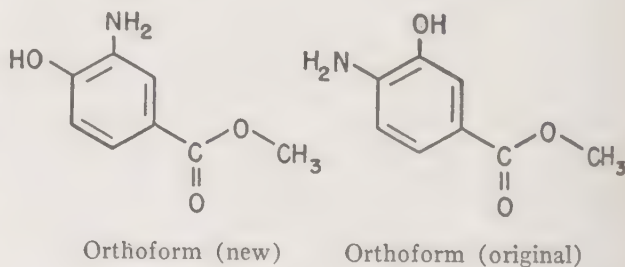
OFFICIAL OCCURRENCE	PER CENT METHYLPARABEN
U.S.P.	
Hydrophilic Ointment	0.025
N.F.	
Methylrosaniline Chloride Jelly	0.026

Propylparaben U.S.P. (Propyl Parahydroxybenzoate, Propylben). This ester is prepared and used in the same manner as methylparaben. It occurs as a white powder or as small, colorless crystals which are only slightly soluble in water (1:2,000) and soluble in most organic solvents. It is used as a preservative, primarily against yeasts (See Methylparaben).

Butoben, *n*-butyl-*p*-hydroxy benzoate, is also a useful preservative against yeast.

OFFICIAL OCCURRENCE	PER CENT PROPYLPARABEN
U.S.P.	
Hydrophilic Ointment	0.015
N.F.	
Methylrosaniline Chloride Jelly	0.014

Orthoform (Orthoform-New) N.N.R. Methyl-*m*-amino-*p*-hydroxybenzoate, Orthoform (Orthoform-New). Orthoform is prepared by esterifying *m*-nitro-*p*-hydroxybenzoic acid with methyl alcohol and reducing the *m*-nitro-ester to the *m*-amino-ester.



About 1909, Einhorn prepared orthoform after his studies on the cocaine molecule. This was the forerunner of esters from *p*-aminobenzoic acid, which have become very useful as local anesthetics (See *p*-aminobenzoic acid derivatives). The original "Orthoform" as synthesized by Einhorn was a *p*-amino-*m*-hydroxy compound. Present-day use of this name refers to the *m*-amino-*p*-hydroxy compound which is described in the N.N.R. and further differentiated by the synonym "Orthoform-New."

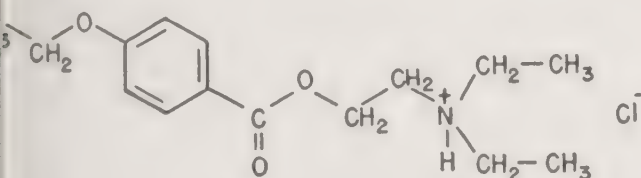
The ester occurs as a fine, white, crystalline powder that is tasteless and odorless; it is insoluble in water but soluble in organic solvents.

Due to its insolubility, the use of orthoform as an anesthetic is restricted principally to powders and ointments. It is ineffective on unbroken skin.

p-ALKOXYBENZOIC ACID DERIVATIVES

Intracaine Hydrochloride (Diethoxin, β -Diethylaminoethyl-*p*-ethoxybenzoate Hydrochloride) is an example of *p*-alkoxy substitution in the local anesthetic compounds of the ester type.

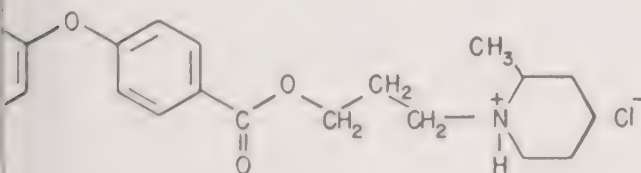
It occurs as a white, crystalline powder, which is water soluble. Tests show it to be less toxic than procaine and about twice as effective intracutaneously, with a longer period of duration. On mucous membranes, it is somewhat superior to procaine. The uses are comparable to those of procaine and it also is available as the free base in oil and ointments. Usually, 0.3 to 1 per cent is used in infiltration procedures.



Intracaine Hydrochloride

p-ARYLOXYBENZOIC ACID DERIVATIVES

Surfacaine (Cyclomethycaine) is a substituted piperidinyllalkyl benzoate hydrochloride.¹⁷



It is an odorless, white, crystalline powder, soluble in water (1:100). The solution is

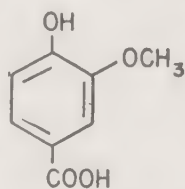
faintly acid, stable, and may be sterilized by boiling or autoclaving at temperatures up to 115° C. In toxicity it is comparable to procaine. Systemic toxicity is rare, and few allergic reactions have been observed.

Surfacaine is an effective local anesthetic on damaged or diseased skin and on rectal mucous membrane. It is useful topically on burns (sunburn), abrasions and mucous membranes, and is most commonly applied in 0.25 to 1 per cent ointments or suppositories.

VANILLIC ACID DERIVATIVES

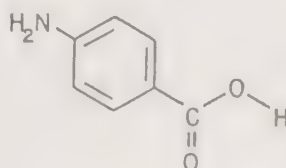
Vanillic Acid Esters.¹⁸ Vanillic acid, known for years, is obtained by the oxidation of vanillin, coniferin or acetyleugenol. Several esters of it with aliphatic alcohols have been prepared and tested as preservatives.

The approximate solubilities in water of the lower alcoholic esters of vanillic acid are: methyl 0.2, ethyl 0.3, propyl 0.075, isopropyl 0.03, butyl 0.02 and isobutyl 0.01 per cent. The preservative effect of the esters was tested against spore-forming bacteria, non-spore-forming bacteria and molds. They were found particularly effective in preventing the growth of the spore-formers and the molds. They are used as are *p*-hydroxybenzoic acid esters or sodium benzoate. These esters are of the same order of toxicity as the benzoate.



p-AMINOBENZOIC ACID DERIVATIVES

p-Aminobenzoic Acid (Amben, PAB, Paba). This acid was early found to be of primary importance in the development of local anesthetics and was not considered in other phases of therapy until about 1940. (See Vitamins, Chap. 28.)



LOCAL ANESTHETICS

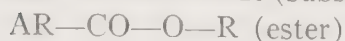
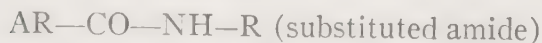
Local anesthetics include several different chemical classes of organic compounds. In general, medicinal compounds that produce local anesthesia are hydroxy-compounds, esters and a miscellaneous group.

Hydroxy-compounds that are useful are mainly in the aromatic series, although some alicyclic hydroxy-compounds possess a little activity. The aliphatic alcohols (those without aryl groups) are useless as local anesthetics. Phenol previously has been mentioned as having local anesthetic properties, as were resorcinol and the cresols. It should be noted, however, that activity decreases and toxicity increases with increased substitution on the aromatic ring (methoxy and hydroxy).

Introduction of a methylene group to separate the aromatic ring from the hydroxy group, as in benzyl alcohol, produces a good local anesthetic without the disadvantages of phenol (q.v.). Also, note that saligenen, β -phenylethyl alcohol and α -phenyl cinnamyl alcohol possess anesthetic properties. Examples of alicyclic alcohols are cyclohexanol and menthol.

The miscellaneous group of local anesthetics includes those compounds that are unrelated chemically and yet exhibit anesthetic properties. Many compounds in this class are recorded in the literature, but relatively few are used in medicine for this purpose. Examples are Nupercaine (an amide), quinine (a cupreine), Eucupin, phenacaine (acetamidine) and Diothane (urethane). Also in this group may be mentioned methyl and ethyl chloride; these compounds produce their effects by freezing the tissue.

Amides and imides may be considered as having the group —NH— substituted for the —O— of an ester:



Active amides in which R represents a dialkylaminoalkyl group are benzamide, *p*-aminobenzamide, cinnamide, naphthoamide

(See Nupercaine). Phthalimides have produced active local anesthesia.

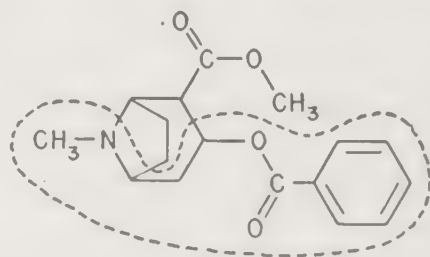
Urethanes or carbamates, when properly substituted, do provide effective compounds.

In the structure
$$\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{N—CO—O—R}^3 \\ \diagup \\ \text{R}^2 \end{array}$$
 it can

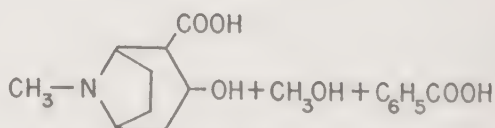
be seen that a variety of compounds might be possible (see Diothane).

The ester group compounds are by far the most important class. The possible number of compounds is large because of the many different alcohols and acids. Since their development was from observation of the cocaine molecule, many significant criteria have been proposed. Two of these are: (1) The ester must contain nitrogen, either in the alcohol, the acid, or in both and (2) the acid must be aromatic and the alcohol is usually aliphatic or alicyclic.

In 1884, Koller¹⁹ observed that cocaine hydrochloride produced anesthesia in the eye. The work of Willstatter on the elucidation of the cocaine molecule then led to the synthesis of hundreds of compounds possessing local anesthetic properties. On hydrolysis, cocaine gives benzoic acid, methyl alcohol and ecgonine. Ecgonine contains an



Cocaine



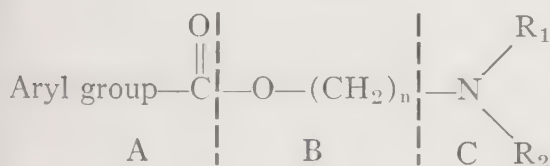
Ecgonine

alcoholic hydroxyl group and a carboxyl group and has the properties of a tertiary amine. On examination, ecgonine can be

seen to be a combined piperidine and pyrrolidine ring. That portion of the cocaine formula enclosed by a dotted line has been found to represent the anesthesiophoric group. By 1890, ethyl *p*-aminobenzoate had been prepared, showing that esters with nitrogen on the acid group possess local anesthetic properties. Soon thereafter, Einhorn prepared orthoform (1909) and procaine (1906). During this same period, studies were made on esters of basic alcohols with benzoic acid, for example, stovaine (1904). (See Table 21.)

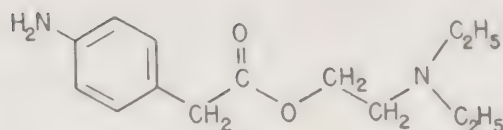
Although many acids (See Table 22) have been used to prepare basic esters, *p*-aminobenzoic has produced the most successful compounds (See Table 23).

The anesthesiophoric group may be represented more simply by the following structure:

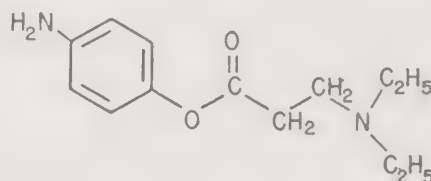


The A portion or acid group includes practically every reasonable available aromatic acid. Benzoic and *p*-aminobenzoic acids have been proven best, and in Table 22 are listed acids of which esters have been prepared and tested. Examination of numbers 2 to 22 indicates how the kind and position of substituents have been varied on the benzene ring. Except for esters of cinnamic acid (No. 34), none of the others have produced a useful local anesthetic. Because of the voluminous literature concerning local anesthetics, the varied types of organic esters and the individual evaluation methods reported by investigators, comparison is almost impossible. A few rules, not too well-established, may be cited from the researches thus far:

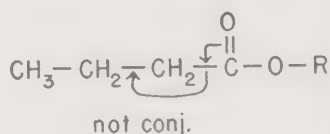
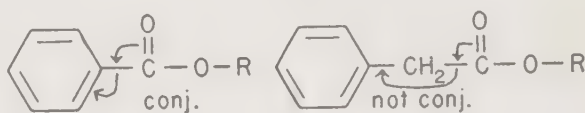
1. Introduction of a methylene group (CH_2), as in phenylacetic acid, decidedly decreases the activity. Note that the following structure is practically inactive:



2. The carboxyl group must be attached to an aryl group. Structures²⁰ such as the following have no local anesthetic action:



3. The carbonyl group must be attached to a conjugated system. Note increase of activity for esters of cinnamic acid over those of phenylacetic and β -phenylpropionic acids. Also, slight local anesthetic activity is observed in esters of acrylic acid; none is observed in propionic acid.



4. The esters of *p*-aminobenzoic acid are more effective than are the esters of benzoic, *p*-hydroxybenzoic and *p*-alkoxybenzoic acid.

5. *p*-Alkoxybenzoates increase in activity as the alkyl group increases in molecular weight.

6. The addition of an amino group in the meta position of *p*-alkoxybenzoates increases activity but also increases toxicity.

7. An alkyl group on the aromatic amino nitrogen increases anesthetic potency and toxicity (Pontocaine). In cases of the sim-

plest esters of *p*-aminobenzoic acid (Benzocaine), when the amino group has a hydrogen replaced by an alkyl group, the activity is lost.

8. The most desirable position of the amino group on the aromatic ring is para to a carboxy group.

9. Most esters of heterocyclic acids possess some local anesthetic properties, except for α -picolinic, nicotinic and quinolinic acids. They decrease in the following order: 29, 30, 31, 27, 32. (See Table 22).

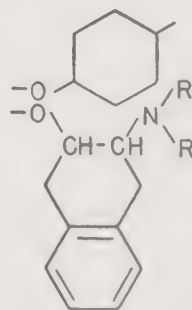
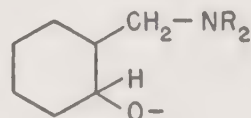
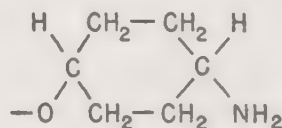
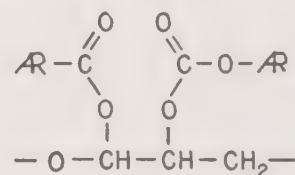
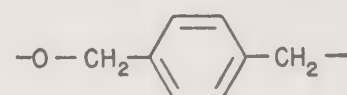
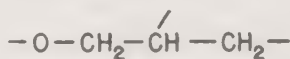
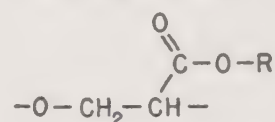
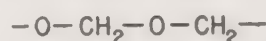
10. Esters of thiolbenzoates have about the same order of action and toxicity as benzoates, but cause some dermatosis.

TABLE 22. SOME AROMATIC ACIDS THAT HAVE BEEN ESTERIFIED FOR LOCAL ANESTHETIC STUDIES

1. Benzoic Acid
2. Phenylacetic Acid
3. Phenylhydroxyacetic Acid
4. Phenylmethylacetic Acid
5. α -phenylpropionic
6. *p*-Toluic Acid
7. Piperonylic Acid
8. *p*-Hydroxybenzoic
9. *p*-(β -hydroxyethyl) Benzoic Acid
10. *p*-(β -ethoxyethyl) Benzoic Acid
11. *p*-Hydroxy-*m*-aminobenzoic Acid
12. Alkoxybenzoic Acid
13. Aryloxybenzoic Acid
14. *p*-Ethylmercaptobenzoic Acid
15. *p*-Halobenzoic Acid
16. *p*-Aminobenzoic Acid
17. *p*-Alkylaminobenzoic Acid
18. *p*-Dialkylaminobenzoic Acid
19. *p*-Aminomethylbenzoic Acid
20. *p*-(Diethylaminoethyl) Benzoic Acid
21. *p*-(Diethylaminoethoxy) Benzoic Acid
22. *p*-Phenylbenzoic Acid
23. α -Naphthoic Acid
24. β -Naphthoic Acid
25. Phthalic Acid
26. 3-Aminophthalic
27. Picolinic Acid
28. Nicotinic Acid
29. α -Carboxypyrrole
30. α -Carboxythiophene
31. α -Carboxyfuran
32. α - β -Dicarboxylquinoline
33. *p*-Aminothiolbenzoic Acid
34. Cinnamic Acid

The B portion or alkyl chain of the alcohol involved in the ester has been the subject of considerable study. Local anesthetics in current use attest to the varied structures that have been found desirable for part B. The chain may not only be branched, as in stovaine, and contain two tertiary amino groups as in alypin, but may include one of the following general types:

STRUCTURES USED IN B PORTION



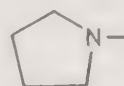
In general, the group $-CH_2-CH_2-CH_2-$ (propylene) provides the most active compounds, with $-CH_2-CH_2-$ (ethylene) next. The group $-CH_2-$ makes the ester too irritant. Only a few compounds

have been prepared where B is $(\text{CH}_2)_4$ or larger. Indications are, however, that there is slight increase in activity in chains containing more than four carbon atoms.

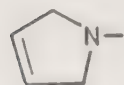
The C-portion represents the amine part of the amino-alcohols used to esterify the aromatic acids. Here again, variation of structures is observed among the local anesthetics in use today. The advantage of the aliphatic amino-nitrogen is its ability to form salts with inorganic acids, thereby providing water-soluble compounds. On this point, some workers have claimed variations in anesthetic activity depending upon the acid salt. Procaine borate is an example, but there is some question as to whether or not it has any advantage over the hydrochloride. Another variation of the acid is employed, for example, in procaine nitrate to avoid incompatibility with silver salts. Butyn is sold as the sulfate because it is more soluble than the hydrochloride.

The amino group always has one or both of its hydrogens substituted. Very little information is available on nonsubstituted amino-alcohol esters except that some are reported unstable. The β -aminoethyl-*p*-aminobenzoate has been reported as having no anesthetic effect in a 5 per cent solution. The most common types are those in which R_1 and R_2 are the same, usually lower alkyl groups (C_5 to C_2). In general, the anesthetic property increases with the size of the alkyl groups, the maximum being at C_3 to C_4 . The groups R_1 and R_2 do not have to be the same and no advantage has been observed when this is true. R_1 and R_2 may also be identical and unsaturated groups or may be hydrogen and an alkyl group (amylsine). Very satisfactory compounds are possible when R_1 and R_2 , together with the nitrogen, form an aliphatic heterocyclic ring. The piperidine ring has proved to elicit strong anesthetic properties (Metycaine). Also studied have been compounds containing the following cyclic structures for Part C:

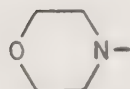
STRUCTURES USED FOR C PORTION



Pyrrolidine



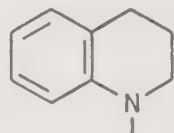
Pyrroline



Morpholine



Thiomorpholine



Tetrahydroquinoline



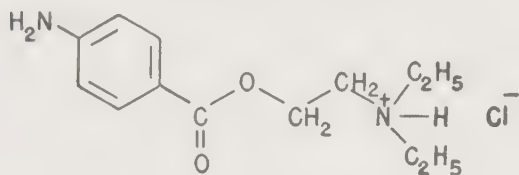
Tetrahydronaphthyl

PROPERTIES

The chemical properties of the ester type of local anesthetics are of prime importance to the pharmacist. Due to the presence of the amino group, the free esters are basic substances, usually oil-like liquids or solids with low melting points. They form alkaline solutions in water and combine with organic or mineral acids to form salts. The free base is only slightly soluble in water but is readily soluble in lipoids and organic solvents. For this reason, the base is used in ointments and oil solutions (Ethylaminobenzoate Ointment U.S.P.). Partly because of the ester structure, but primarily due to the *p*-amino group, they are unstable to heat, light and oxidation.

Salt formation of the basic ester is com-

parable to that of ammonia. The addition of an acid (hydrochloric acid) to a local anesthetic (procaine), to form the hydrochloride, is expressed as follows:

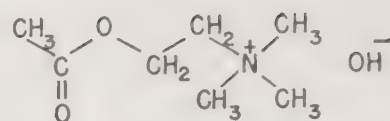


The hydrochloride, which occurs as a white, crystalline powder, is the salt most popular for medical use, although the nitrate, sulfate and borate are also used in special circumstances, for example to avoid incompatibilities such as soluble silver with chlorides. These acid salts are very soluble in water or alcohol but are only slightly soluble in lipoids and organic solvents.

In aqueous solution they ionize as do the ammonium salts, producing a solution having a pH of 4 to 6. This varies, of course, with the local anesthetic base and the acid used. The free base is liberated when alkaline substances such as hydroxides, carbonates and bicarbonates or any other normal salt that is alkaline are added to a solution of the salt. Since local anesthetics are alkaloidlike they often are precipitated by the alkaloidal reagents (See Chapter 27).

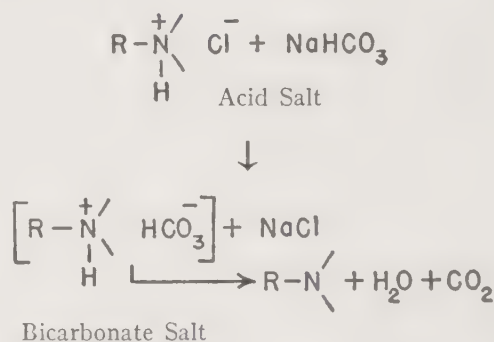
MODE OF ACTION

The mode of action for local anesthetics may follow along the lines of Dodds' (see Stilbestrol) and Woods' (see Sulfanilamide) explanations for the function of estrogenic steroids and *p*-aminobenzoic acid, respectively. A considerable amount is known about the chemical structure of local anesthetics, so one may look for a natural substrate associated with nerve function. Acetylcholine combines with a "receptor molecule" causing the stimulation at a nerve termination or at the synapse in the cholinergic nerve. This combination must have a relation to the chemical structure of acetylcholine.



The ester type of local anesthetics such as procaine, due to its structural similarity, seems to be able to combine with the same receptor as does acetylcholine. In the case of local anesthetics, however, the combination does not produce stimulation. Instead, it results in insensitivity of the nerve and consequently anesthesia.

The compounds also may function according to the Meyer-Overton law since the free base is lipid soluble. Perhaps the base is liberated by the slightly alkaline fluids in the tissues. First to be formed in the tissue fluids is the soluble bicarbonate salt that slowly breaks down to the free base, carbon dioxide and water.



It has been observed that a neutral or basic solution of procaine, obtained by using sodium bicarbonate, has a greater effectiveness than does a solution of the hydrochloride. This indicates that neutralization of the acid salt is, perhaps, a preliminary step to action.

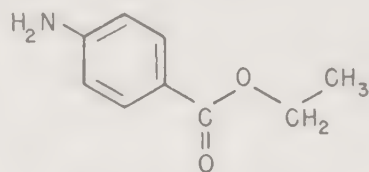
Most local anesthetic drugs, when administered, gain entrance into the body by absorption and are destroyed by the liver.

Most of the compounds that have a local anesthetic action do not possess the property of vasoconstriction. Cocaine, however, does possess each property in sufficient degree so that actual contact with nervous tissue is prolonged. This lack of constriction of blood vessels speeds absorption and explains the

short duration of anesthesia obtained from the synthetic compounds. In 1903, Braun suggested the addition of epinephrine hydrochloride or other vasoconstrictors to solutions of local anesthetics. This is now standard practice and concentrations of 1:25,000 to 1:50,000 are the rule. Not only is anesthesia prolonged, but the rate of absorption is reduced, thus allowing time for detoxication before a toxic concentration can be built up in the circulation.

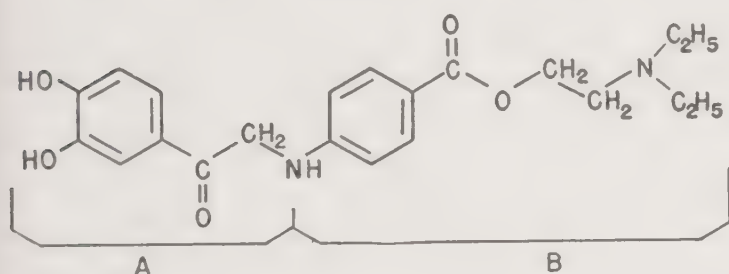
From time to time, some investigators endeavor to prepare a compound having local anesthetic and vasoconstrictive properties. Some are recorded in the literature, but, actually, the combination of these qualities is of questionable value. An example²¹ is "Epicaine," a combination of a pressor

It occurs as a white, odorless, crystalline powder, stable in air. It is soluble in organic solvents, fixed oils or mineral acids and insoluble in water and alkaline solutions.



Ethyl Aminobenzoate

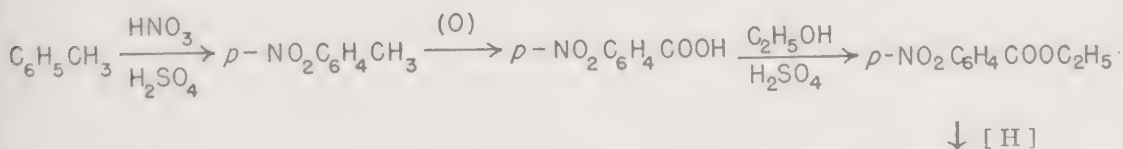
Benzocaine is destroyed when boiled with water, but its oil solutions may be boiled without change. It forms a sticky mass with resorcinol and forms colored mixtures with bismuth subnitrate. A hydrochloride is



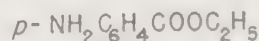
residue (A) and an anesthetic residue (B).

Table 23 (page 206) shows the local anesthetics that are esters of *p*-aminobenzoic acid.

Ethyl Aminobenzoate .(Benzocaine) U.S.P. (Anesthesin, Parathesin). The ester, Ethyl Aminobenzoate, was prepared soon after the discovery of Orthoform (q.v.). It is readily prepared synthetically by several procedures,²² of which the following is typical:



It may also be prepared by reacting *p*-nitrobenzoyl chloride with ethyl alcohol to form ethyl *p*-nitrobenzoate, which is then reduced to ethyl *p*-aminobenzoate.



insoluble in aqueous media, there is sufficient

TABLE 23. LOCAL ANESTHETICS THAT ARE ESTERS OF *p*-AMINOBENZOIC ACID

$\begin{array}{c} \text{O} \\ \parallel \\ \text{---} \text{C} - \text{O} \text{---} \end{array}$ $\begin{array}{c} \text{---} \text{C}_6\text{H}_4 \text{---} \end{array}$ $\text{---} \text{R} \text{---}$			
H ₂ N—	Ethyl Aminobenzoate	—CH ₂ —CH ₃	
H ₂ N—	Propaesin	—CH ₂ —CH ₂ —CH ₃	
H ₂ N—	Butyl Aminobenzoate	—CH ₂ —CH ₂ —CH ₂ —CH ₃	
H ₂ N—	Procaine	—CH ₂ —CH ₂ —	—N $\begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \\ \text{iso C}_3\text{H}_7 \end{cases}$
H ₂ N—	Isocaine	—CH ₂ —CH ₂ —	—N $\begin{cases} \text{C}_2\text{H}_5 \\ \text{iso C}_3\text{H}_7 \\ \text{iso C}_3\text{H}_7 \end{cases}$
H ₂ N—	Butacaine	—CH ₂ —CH ₂ —CH ₂ —	—N $\begin{cases} \text{C}_4\text{H}_9 \\ \text{C}_4\text{H}_9 \end{cases}$
$\begin{array}{c} \text{H} \\ \diagup \\ \text{N} \\ \diagdown \\ \text{C}_4\text{H}_9 \end{array}$ —	Tetracaine	—CH ₂ —CH ₂ —	—N $\begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$
H ₂ N—	Panthesine	—CH ₂ —CH—CH ₂ —CH(CH ₃) ₂	—N $\begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases}$
H ₂ N—	Larocaine	—CH ₂ —C(CH ₃) ₂ —CH ₂ —	—N $\begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases}$
H ₂ N—	Tutocaine	—CH(CH ₃)—CH(CH ₃)—CH ₂ —	—N $\begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$
H ₂ N—	Monocaine	—CH ₂ —CH ₂ —	—N $\begin{cases} \text{iso C}_4\text{H}_9 \\ \text{H} \end{cases}$
H ₂ N—	Amylsine	—CH ₂ —CH ₂ —	—N $\begin{cases} \text{C}_5\text{H}_{11} \\ \text{H} \end{cases}$

absorption through abraded surfaces and in ulcerative conditions of the digestive mucous membranes so that it acts almost entirely on the nerve terminals. Cocaine, in contrast, is thought to affect the nerve trunk. Benzocaine is used for the local anesthetic action in powders up to 20 per cent, in ointments up to 10 per cent, in suppositories and for various types of surface pain and itching. Some use is made of it in throat lozenges and tract.

The average dose is 0.3 Gm.

OFFICIAL OCCURRENCE

PER CENT
BENZOCAINE

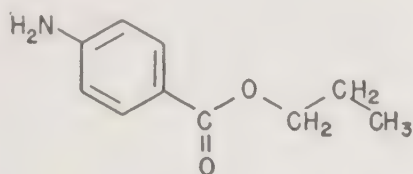
U.S.P.

Ethyl Aminobenzoate Ointment... 5.0

N.F.

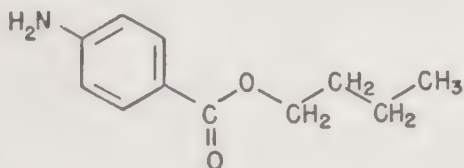
N.F. Sun Cream 2.0

Propaesin (Propyl Aminobenzoate) is the ester from propyl alcohol and *p*-aminobenzoic acid. It has properties and uses very similar to those of benzocaine. This compound is present in some proprietary suppositories.



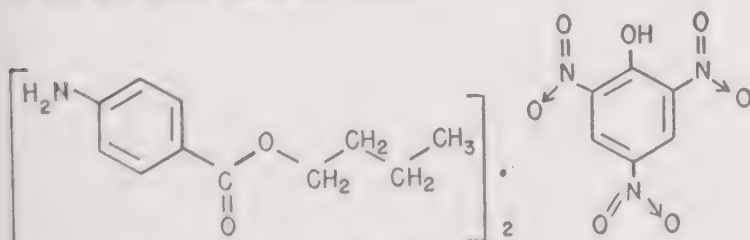
Propaesin

Butyl Aminobenzoate (Normal Butyl Aminobenzoate) U.S.P. (Butesin) is the butyl analogue of benzocaine, using butyl alcohol in place of ethyl alcohol. It occurs as a white, crystalline powder that is tasteless and odorless. The solubilities and incompatibilities are the same as those for ethyl aminobenzoate. Butesin is used in the same way as anesthesin and is claimed to be more effective; however, it is more toxic too. Application of it is usually in the form of the picrate.



Butyl Aminobenzoate

Butamben Picrate (N.N.R.) [(Di-*n*-butyl-*p*-aminobenzoate) Trinitrophenol] is thought to contain two moles of butesin and one of picric acid. It occurs as a yellow, amorphous powder that is slightly soluble in water (1 to 2,000) and soluble in fixed oils or organic solvents. Note that this is the reverse of all the other local anesthetics.

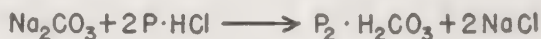


Butamben Picrate

In a saturated aqueous solution it is used in the eye, and, as a 1 per cent ointment, for burns and denuded areas of the skin. A disadvantage is that the yellow color will stain the skin and clothing.

Procaine Hydrochloride (Procaine) U.S.P. (Novacaine, Neocaine, Planocaine, Ethocaine). Procaine is one of the oldest and most used of the synthetic local anesthetics, having been developed by Einhorn in 1906. A synthesis may be carried out as shown at the top of page 208.

The free ester is an oil, but it is isolated and used as the hydrochloride salt. It occurs as an odorless, white crystalline powder that is stable in air (see properties of local anesthetics). Although most alkalies will precipitate the free base, sodium bicarbonate will not.

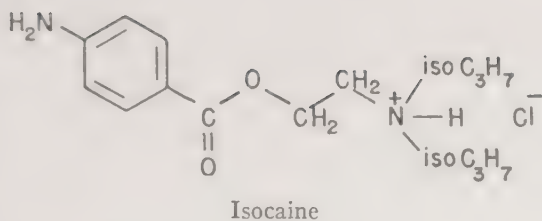


1 Mole 2 Moles

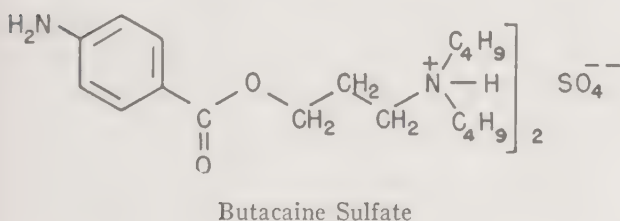
When no excess of sodium carbonate is present, the procaine carbonate is soluble, but it soon breaks down, with precipitation of the procaine base.



Sodium carbonate in excess causes an immediate precipitation of the procaine base. Sodium bicarbonate, on the other hand, whether or not in excess, will form the soluble salt, procaine bicarbonate, that is stable for several days and then will decompose slowly to procaine, carbon dioxide and water.

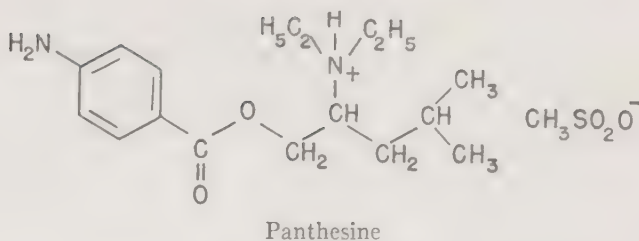


Butacaine Sulfate U.S.P. (Butyn Sulfate, Di-*n*-butylamino-propyl-*p*-aminobenzoate Sulfate). Butyn is similar to procaine except that the amino-alcohol used in synthesis is di-*n*-butylaminopropanol. The

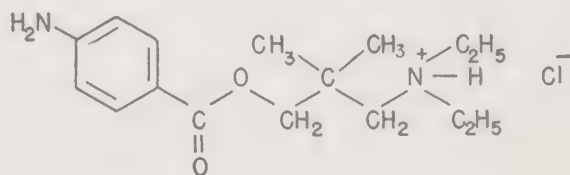


sulfate is an odorless, white crystalline powder that is tasteless and has the same solubilities and incompatibilities as procaine. In this case, the sulfate salt is prepared and used because the hydrochloride is less soluble. It resembles cocaine in action and, intravenously, has the same toxicity; it is, however, more toxic on subcutaneous use. Today it largely has replaced cocaine because it possesses all of the advantages and none of the disadvantages of the natural alkaloid. Solutions of butyn may be sterilized by boiling and are effective on mucous membrane and in the eye. It is the local anesthetic of choice for use in the eye since it has few side effects and does not cause mydriasis. Usually, a 2 per cent solution is applied topically for use in the eye, nose and throat.

Panthesine. This is an ester of *p*-aminobenzoic acid and the amino-alcohol, diethylaminoleucinol, made soluble by forming the methanesulfonate salt. Its solutions can be sterilized by boiling and are used for surface and infiltration anesthesia. It is less toxic than cocaine. The free base is marketed in a 5 per cent ointment.

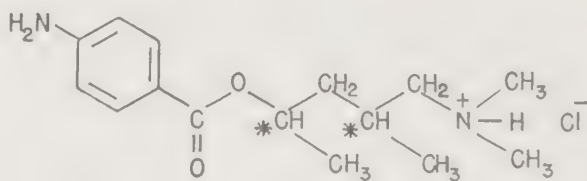


Larocaine Hydrochloride (*p*-Aminobenzoxy-2,2-dimethyl-3-diethylaminopropanol Hydrochloride).



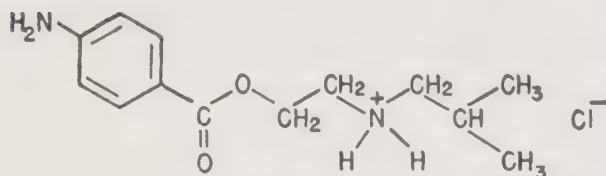
The hydrochloride is a white, crystalline powder, freely soluble in alcohol or water and insoluble in oils and organic solvents. Its solutions are acid in reaction and will decompose if boiled more than fifteen to twenty minutes. It is comparable in effectiveness to butacaine sulfate for use in the eye and on mucous membrane. The action is quick and of longer duration than that of procaine or cocaine. Due to the high order of toxicity, it is used cautiously by injection.

Tutocaine Hydrochloride (Butamin, δ -Dimethylamino- α,β -dimethylbutyl-*p*-aminobenzoate Hydrochloride).



Tutocaine hydrochloride is produced and used as a racemic mixture since it has two asymmetric carbon atoms (*). The salt occurs in odorless, white crystals. It is used primarily for surface anesthesia in 0.25 to 2 per cent solutions in the eye, nose, throat or genito-urinary tract. Solutions of the salt may be sterilized with heat. It is fairly rapid and prolonged in its action.

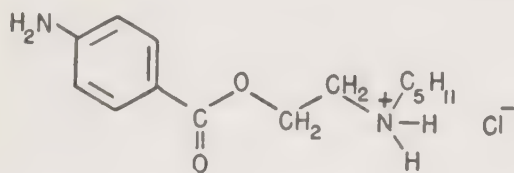
Butethamine Hydrochloride N.N.R. (Isobutylaminoethyl *p*-aminobenzoate) is a soluble, white, crystalline powder. It has properties and uses similar to procaine, and is about three times as potent. It is not recommended for topical use. Usually solutions of 1 to 2 per cent are employed.



Butethamine Hydrochloride

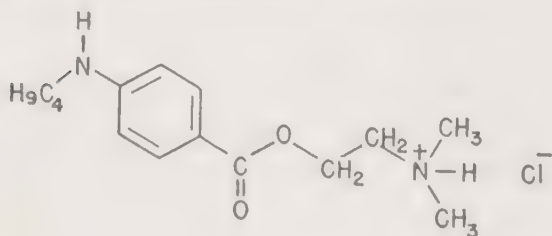
Butethamine Formate N.N.R. This salt is especially suggested for use in spinal anesthesia. The dose is about three-fourths of that used for procaine.

Amylsine Hydrochloride (Amylcaine Hydrochloride) N.N.R. (Amylaminoethyl *p*-Aminobenzoate, Aminocaine).



This salt occurs as a white, crystalline powder which is used in 2 to 4 per cent solution in ophthalmology when mydriasis is to be avoided. Its activity resembles that of cocaine and at the present time its use is restricted to corneal anesthesia. The name was recently changed to Amylsine Hydrochloride to avoid confusion with another compound, called Amylcaine Hydrochloride, in the British Pharmacopoeia.

Tetracaine Hydrochloride . (Amethocaine Hydrochloride) U.S.P. (Pontocaine, Hydrochloride N.N.R., Pantocaine, Anethaine, Deciane, β -Dimethyl-aminoethyl *p*-*n*-butylaminobenzoate Hydrochloride).

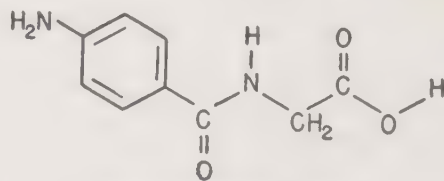


Tetracaine is so named because it contains two groups of four (tetra) carbon atoms each. It differs from the other local anesthetics in having a substituent (butyl) replace a hydrogen on the *p*-amino nitrogen of *p*-aminobenzoic acid. An aqueous solution may be sterilized by boiling. If it is made neutral or slightly basic, decomposition results.

Tetracaine resembles procaine for infiltration anesthesia and approaches the effectiveness of cocaine for topical use. In concentrations ranging from 0.5 to 2 per cent it is used in the eye and is the drug of choice for the nose and throat. A 1 per cent solution may be employed for spinal anesthesia where the effectiveness is very prolonged.

Table 24 (page 211) shows the properties of some local anesthetics.

***p*-Aminohippuric Acid (PHA, 4-Aminobenzoylglycine)**, is an acid readily prepared from *p*-nitrobenzoyl chloride and glycine. The *p*-nitro acid is isolated and reduced. It is excreted by the kidney upon the ingestion of *p*-aminobenzoic acid or its esters.



p-Aminohippuric Acid

It occurs as a white, crystalline powder which is slightly soluble in water or alcohol and soluble in organic solvents.

The sodium salt is excreted by the tubular epithelium of the kidney and by the glomerulus, thus serving as a means of measuring the effective renal plasma flow and of determining the functional capacity of the tubular excretory mechanism.

It is supplied as the sodium salt in ampules or as the free acid.

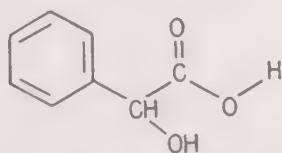
MANDELIC ACID DERIVATIVES

Mandelic Acid (Racemic Mandelic Acid) N.F. Mandelic Acid usually is prepared from benzaldehyde and hydrogen cy-

TABLE 24. PROPERTIES OF SOME LOCAL ANESTHETICS

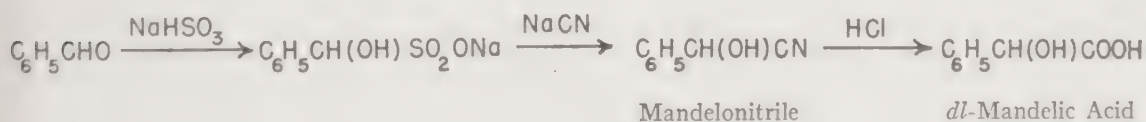
LOCAL ANESTHETIC	SOLUBLE IN		WHITE CRYST. POWDER	RELATIVE POTENCY		STABLE TO HEAT	USE	
	WATER	ALCOHOL	ORGANIC SOLVENT	COCAINE	PROCAINE		INFILTRA- TION	TOPICAL
Amydricaine. HCl	+	+	—	+	1.0	3.0	—	+
Amylsine. HCl	...	...	...	...	...	2.0	...	Toxic
Apothesine. HCl	+	+	—	+	...	0.12	+	+
Butacaine. H ₂ SO ₄	+	+	—	+	1.5	...	+	+
Butesin Picrate	—	+	+	—	...	...	—	+*
Butyl Aminobenzoate ..	—	+	+	+	1.5	...	—	+
Cocaine	+	+	—	+	1.0	...	+	+
Diothane. HCl	+	+	—	+	2.0	...	...	+*
Ethyl Aminobenzoate ..	—	+	+	+	...	...	—	+*
Eucaïne	+	+	—	...	0.5	...	...	...
Eucupin	—	+	+	+	0.5	...	—	+
Intracaine. HCl	+	+	—	...	2.0	...	+	fair
Isocaine. HCl	+	+	—	...	2.0	...	+	fair
Larocaine. HCl	+	+	—	+	2.0	...	—	+
Metycaine. HCl	+	+	—	+	0.5	...	+	+*
Monocaine. HCl	+	+	—	...	...	3.0	—	—
Nupercaine. HCl	+	+	—	+	20.0	...	...	+*
Orthoform	—	+	+	...	...	...	—	+
Panthesine. CH ₃ SO ₄ ...	+	+	—	+	...	...	+	+
Phenacaine. HCl	+	+	—	...	1.5	...	...	+
Procaine. HCl	+	+	—	+	...	1.0	—	—
Propaesin	slight	—	+	+	...	...	—	+
Stovaine. HCl	+	+	—	+	0.75	...	+	—
Surfacaine. HCl	+	+	—	+	...	1.0	+	+
Tetracaine	+	+	—	+	15.0	...	+	+
Tutocaine. HCl	+	+	—	+	4.0	...	+	+

* The base or salt is used in ointments.



Mandelic Acid

anide or sodium cyanide. The solid sodium cyanide has the advantages of being easier to handle, less likely to be toxic. The following equation illustrates the reaction steps:



In bitter almonds there occurs the glucoside, amygdalin, which is the gentiobioside of mandelonitrile. On hydrolysis, this nitrile yields *l*-mandelic acid (see Glycosides).

The acid occurs as a white, crystalline

powder which may be odorless or have a slight aromatic odor. Upon exposure to light, the crystals slowly darken and decompose.

In 1935,²⁴ Fuller announced the isolation of β -hydroxybutyric acid from the urine of patients with uncontrolled diabetes and also from urine excreted by individuals on a ketogenic diet. Previous to Fuller's work,

the freedom from infections of the urinary tract among diabetics had been observed, as well as the stability or resistance to putrefaction of diabetic urine. Due to these

observations, the ketogenic diet was used in the treatment of upper urinary tract infections. β -Hydroxybutyric acid is an oxidation product of fatty acids in the course of their conversion to carbon dioxide and water, and is, therefore, a normal metabolite. Since the acid is metabolized, oral administration was not feasible because it would be further oxidized before excretion in the urine could take place.

Rosenheim,²⁵ in an effort to find a suitable acid (β -hydroxyacid) found that mandelic acid possessed good bacteriostatic and bactericidal properties (e.g., for *Escherichia coli*, *Streptococcus faecalis*, *Salmonella*, etc.) and yet, on oral administration, was excreted in the urine, because of a non-metabolizable molecule. Further studies²⁶ indicated that in urine of pH 5.5 or less, mandelic acid was most effective as a urinary antiseptic in such cases as cystitis and pyelitis. Pharmaceutical forms are mandelic acid with ammonium chloride, sodium mandelate with ammonium chloride, calcium mandelate with ammonium chloride, calcium mandelate, methenamine mandelate and mandelates with sodium biphosphate. Other substances to aid in maintaining an acid urine are ammonium nitrate and nitrohydrochloric acid. These are prepared in syrups, elixirs and tablets.

Mandelic acid preparations are less extensively used today because of the introduction of the sulfa compounds.

The average dose is 3 Gm.

Ammonium Mandelate Syrup is a palliative preparation containing approximately 40 grams of mandelic acid and 4.5 grams of ammonia in each 100 cc. Ammonium chloride therapy is not usually necessary but it is often used. The ammonium salt, like that of sodium mandelate, is prone to cause nausea.

The average dose is 4 cc.

Calcium Mandelate U.S.P. Calcium mandelate is readily prepared by using a soluble calcium salt and mandelic acid in an aqueous medium. The compound is crystallized from

water and occurs as a white, odorless powder which is only slightly soluble in water and is insoluble in alcohol.

The calcium salt, being quite insoluble, is nearly tasteless and thus produces less gastric irritation than does either the sodium or ammonium salt. In the intestine, the mandelates all behave the same way, by hydrolyzing, and so liberate free mandelic acid that is excreted in the urine.

The average dose is 4 Gm.

Hexydaline (Mandelamine, Methenamine Mandelate) is a stable complex of methenamine (48 per cent) and mandelic acid (52 per cent). It is very successful in the treatment of common urinary tract infections. It is a white, crystalline powder that is soluble in alcohol or water.

TROPIC ACID DERIVATIVES²⁷

Esters of tropic acid were synthesized after the elucidation of the structure of the atropine molecule. It was early found that atropine had an antispasmodic action, primarily of the neurotropic type. Also, it was observed that the alkaloid, papaverine (q.v.), had a musculotropic type of antispasmodic action. Intensive research has been conducted with the object of developing a single molecule having both types of antispasmodic action. Such a compound should also have a higher therapeutic index and fewer undesirable side effects.

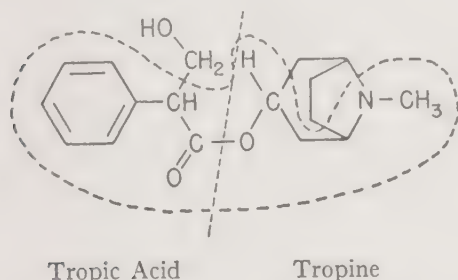
Studies relating to the papaverine structure thus far have not been too successful (See benzyl group, sestron, cyverine and papaverine-related compounds).

Compounds which might be considered as being related to atropine have shown a little more success as antispasmodics possessing both types of action. However, neither field of study approaches the variety, number or success of compounds related to cocaine.

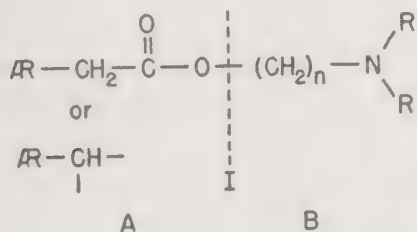
Atropine, in contrast to cocaine, has very weak local anesthetic action, while cocaine has practically no antispasmodic action. On examination outside of the carbomethoxy group for cocaine, the difference lies in the

fact that tropic acid is found in atropine and benzoic acid in cocaine. Perhaps a reason for the slight local anesthetic action of atropine is that in tropic acid the carboxyl-carbonyl group is not in a conjugated double-bond system with the aromatic ring (See Apothecin and Rule 3). Also, the hydroxyl group may interfere since tropic or mandelic acids do not produce satisfactory local anesthetics. External preparations of belladonna and atropine were once used for the local anodyne effect produced.

These preparations are not used much in therapy today.



The portion of the atropine formula enclosed by dotted lines was recognized early as the structure responsible for the spasmolytic action.

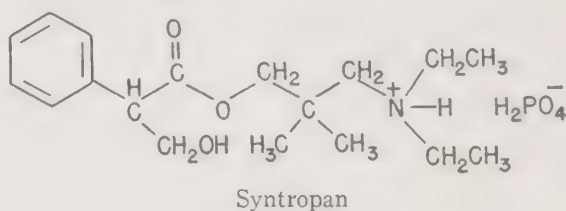


Structure I shows the active portion in the simplest form, where B represents the amino-alcohol (Tropine) part, which is thought to determine intensity of action, and A represents the acid (Tropic Acid) part, usually an arylaliphatic acid, which is thought to determine the nature of action.

All of these are basic esters and usually are marketed as the hydrochloride or some other salt. (See properties of local anesthetics.) These salts are usually white, crystalline powders. The synthetic compounds of the antispasmodic class, like those of local

anesthetic action, are the best ones selected from a related series.

Syntropan (*dl*-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol) N.N.R. is prepared from tropic acid and the same dialkylamino alcohol as that used for Larocaine. It occurs as a white, crystalline powder, soluble in water or alcohol, insoluble in organic solvents and having a bitter taste and faint odor.

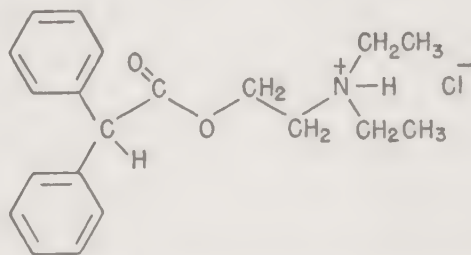


Syntropan is about 20 times less effective than atropine in neurotropic action. It does, however, have the advantage of exerting a musculotropic action. There are practically no side effects such as mydriasis, salivation and changes in cardiac rate that are associated with atropine therapy. It is used primarily as an antispasmodic on smooth muscle such as that of the gastro-intestinal tract, the urethra and the uterus.

The average dose is 50 mg.

DIPHENYLACETIC ACID DERIVATIVES

Trasentine Hydrochloride²⁸ (Adiphenine, Diethylaminoethyl Diphenylacetate Hydrochloride).



The ester is prepared from the acid chloride and the amino-alcohol. Trasentine occurs as white, crystalline needles that are stable but will hydrolyze in solution upon standing. The salt is soluble in water or alcohol and insoluble in organic solvents.

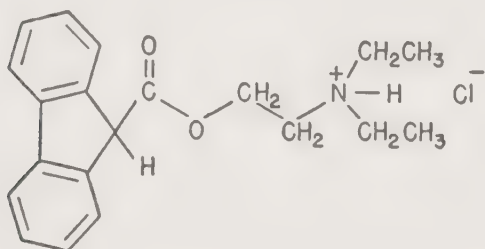
It has about one-twenty-fifth the activity of atropine, but is equal to papaverine as an antispasmodic. Toxicity is equal to, or slightly more than, that of atropine.

Like Syntropan, it has very slight side reactions and is used for the same conditions.

The average dose is 75 to 150 mg.

FLUORENE-9-CARBOXYLIC ACID DERIVATIVES²⁹

Pavatrine (β -Diethylaminoethyl Fluorene-9-carboxylate Hydrochloride).



Pavatrine is reported to be one-seventh as active as atropine and one and one-half times as active as papaverine. It has a negligible mydriatic effect and only slightly depresses the secretory organs. Its uses are similar to those of Syntropan and Trasentine.

The average dose is 150 mg.

CHEMICAL CONSTITUTION AND MYDRIASIS³⁰

Mydriatics are usually of two types: (1) esters of a hydroxy acid and an amino-alcohol (atropine, homatropine) or (2) aryl-alkylamines similar in structure to epinephrine or ephedrine. The first type is the most useful for the dilation of the iris.

Recent research, using various types of organic acids and amino-alcohols, has established certain criteria necessary for mydriasis. These are presented in tabular form on page 215.

1. Although homatropine is an ester of mandelic acid (phenylhydroxyacetic acid), none of ten esters showed any mydriatic activity (Structure II.)

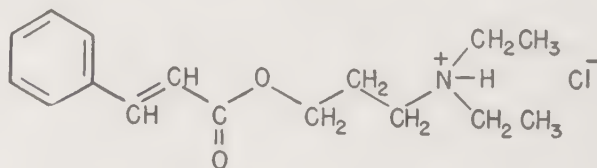
2. Esters of structures III, IV, V and VI do not show any significant activity.

3. The best esters are those of structure I. This shows not only that the hydroxyl group is essential for mydriasis, but also that it may be tertiary. Since Trasentine does not cause mydriasis, it is interesting to compare this formula with structure I.

4. The amino-alcohols that have been found most active with structure I are: (a) $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, (b) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$, (c) $-\text{CH}_2\text{CH}_2\text{NC}_5\text{H}_{10}$ (piperidylethyl).

CINNAMIC ACID DERIVATIVES

Apothesine Hydrochloride (γ -Diethylaminopropyl Cinnamate).



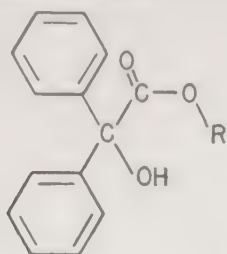
This structure is the only usable ester type of local anesthetic in which the aryl group is not directly attached to the carboxyl group. If β -phenylpropionic acid is used, the ester has no local anesthetic effect; the conjugated double bond, therefore, appears to be necessary.

The ester is slightly more toxic than procaine. Its solutions may be sterilized by boiling, and it is used in 0.5 to 2 per cent concentration, similarly to the way procaine is used.

IDOAROMATIC ACID DERIVATIVES

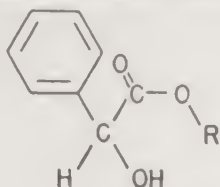
Hippuran (Sodium *o*-Iodhippurate) N.N.R. Dried hippuran contains between 34.95 and 38.8 per cent of iodine. Hippuran is prepared from *o*-iodotoluene, which is oxidized to *o*-iodobenzoic acid and condensed with glycine. It is a white, crystalline powder having an alkaline taste and a slight odor. The crystals are soluble in water, alcohol and in dilute alkali. Aqueous solutions are neutral or slightly alkaline to litmus.

CONSTITUTION OF MYDRIATICS



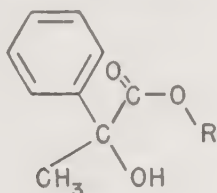
Best ones:
 $R = -CH_2CH_2N(C_2H_5)_2 \cdot CH_3Br$
 $R = -CH_2CH_2NC_5H_{10} \cdot HCl$

I. Benzilic Acid



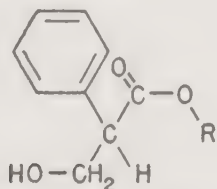
None of ten esters found active.

II. Phenylhydroxyacetic Acid



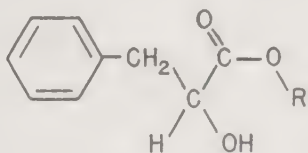
Some activity:
 $R = -CH_2C(CH_3)_2CH_2N(C_2H_5)_2 \cdot H_3PO_4$

III. α-Phenyl-α-hydroxypropionic Acid



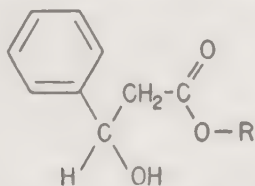
Some activity:
 $R = -CH_2C(CH_3)_2CH_2N(C_2H_5)_2 \cdot H_3PO_4$

IV. α-Phenyl-β-hydroxypropionic Acid



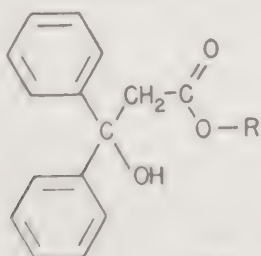
None of five esters active.

V. β-Phenyl-α-hydroxypropionic Acid



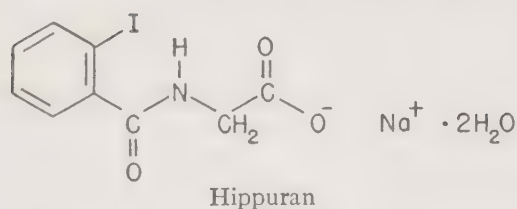
None of seven esters active.

VI. β-Phenyl-β-hydroxypropionic Acid



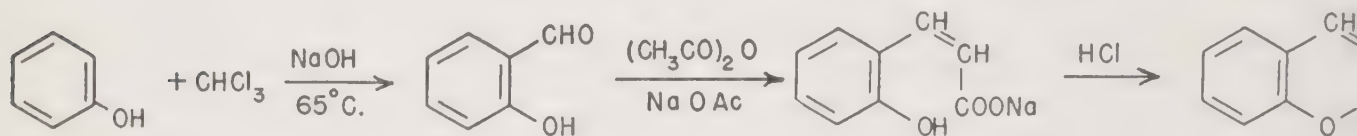
Slightly active:
 $R = -CH_2CH_2N(C_2H_5)_2 \cdot HCl$

VII. β,β-Diphenyl-β-hydroxypropionic Acid

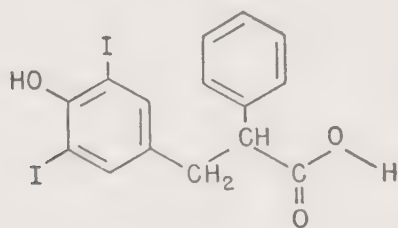


Hippuran is suggested as a radiopaque agent for intravenous, oral or retrograde urography.

Average Dose: intravenous—12 Gm. in 25 cc. water; oral—12 Gm. in 75 cc. of simple syrup.



Iodoalphonic Acid [Priodax, Glaxo, Bili-selectan, Pheniodol, 3-(4-Hydroxy-3,5-di-iodophenyl)-2-phenylpropionic acid]. Priodax may be thought of as a phenyl and benzyl substituted acetic acid. Priodax is not a dye and is not a phenolphthalein derivative. It should be noted in this regard that laxative effects of priodax are rare. The acid occurs as an odorless, tasteless, white or slightly yellow powder that is soluble in alcohol, ether or alkaline solutions. Even though it is insoluble in water, it produces bitter-tasting soluble salts when mixed with salivary juices.



Iodoalphonic Acid

Iodoalphonic acid is employed as a gall-bladder contrast media (cholecystography). Advantages claimed are that it causes less nausea, vomiting and diarrhea.

In preparing dispersions of the powder in a liquid medium it is essential that the mixture be free from all lumpiness.

The average dose is 0.5 Gm.

LACTONES

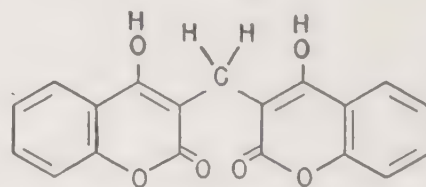
Coumarin N.F. (Cumarin Anhydride, *o*-Oxycinnamic Anhydride, Tonka Bean Camphor). Coumarin is the lactone of ortho-hydroxycinnamic acid. It is a very fragrant material, present in newmown hay and in tonka beans. It is found in the form of glycosides (See Chapter 25) in many plants and may be synthesized according to the following scheme:

Coumarin exists as aromatic, colorless crystals having a burning taste. It is slightly soluble in water and insoluble in organic solvents.

The lactone is used, primarily for its odoriferous qualities in such products as iodoform preparations, aromatic castor oil and imitation vanilla extracts.

OFFICIAL OCCURRENCE	PER CENT COUMARIN
N.F.	
Aromatic Castor Oil.....	0.01
N.F. Sun Cream.....	0.1

Dicumarol* N.N.R. [Dicumarin, 3-3'-Methylene-bis-(4-hydroxycoumarin)].



In 1922 there was reported a cattle disease called "hemorrhagic sweet clover disease," and again in 1931 a study of the disease was made. About 1940 Link,³¹ began his researches on the isolation and synthesis of this factor (Dicumarol) that developed in spoiled sweet clover. Dicumarol is a white, crystalline material that can reproduce the

* Dicumarol is the registered collective trademark of the Wisconsin Alumni Research Foundation, which controls the use thereof.

hemorrhagic disease caused by the naturally occurring substance. As a substitute for heparin in the treatment and prophylaxis of thrombosis, it has the advantages of being readily synthesized and effective after oral administration. However, it is very slow and does not become effective for two or three days, thus it is unsatisfactory in replacing heparin in emergencies.

The mode of action appears to be an inhibition of the synthesis of prothrombin, or a component thereof, and it seems to cause an inability of the body to utilize Vitamin K. Vitamin K and dicumarol are similar in structure and one may supplant the other in an enzyme system. Dicumarol does not affect the clotting power of either blood or plasma in vitro. When ingested by the rat, dicumarol induces hypoprothrombinemia which is counteracted by vitamin K, given either before the anticoagulant is fed, along with it or twelve hours afterward.

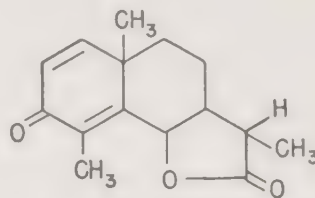
Toxic effects are rare and dicumarol may be used with such drugs as sulfathiazole, barbiturates and morphine. Disease conditions such as pneumonia and tuberculosis do not preclude its administration.

The average dose is 0.25 to 1.0 Gm.

Santonin N.F. (Santolactone). "Santonin is the inner anhydride (lactone) of santoninic acid." It may be considered as an oxygen-containing derivative of a bicyclic sesquiterpene. A process used to supply the drug is to treat wormseed (*Artemisia maritima* var. *anthelminticum* Linné, or any var. of *Artemisia*) with calcium hydroxide, thus forming calcium santoninate. The sodium salt is prepared and is treated with sulfuric acid to convert the sodium salt to santonin. It is deposited as white or colorless crystals which soon become yellow on exposure to light. The lactone is insoluble in water and soluble in organic solvents, forming yellow solutions.

Santonin has a definite anthelmintic action against worms of the ascarides family (roundworms). The action is one of rendering the worm unable to move normally and

thus causing it to be carried out of the bowel in the feces. Structures having the lactone ring have been found to possess anthelmintic properties.



Santonin

The average dose is 0.06 to 0.2 Gm.

OFFICIAL OCCURRENCE

N.F.

Santonin and Mild Mercurous Chloride
Tablets

Santonin Tablets

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16

Aromatic Nitrogenous Compounds

PROPERTIES OF PRESSOR AMINES

MODE OF ACTION OF THE SYMPATHOMIMETIC AMINES

AMINES

PRIMARY AMINES

SECONDARY AMINES

RELATIONSHIP BETWEEN STRUCTURE AND PHYSIOLOGIC ACTIVITY

TERTIARY AMINES

QUATERNARY AMINES

AMIDES

COAL TAR ANALGESICS RELATED TO ACETOPHENETIDIN

POLYAMIDES

AMIDINES

GUANIDINE

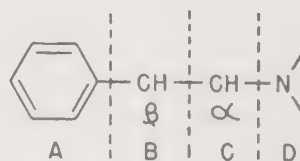
Aromatic and aromatic-aliphatic nitrogenous compounds include the amines and the amides that have an aromatic group in their structure.

The amides present structures having varied physiologic response, such as analgesia and local anesthesia.

In the amine series, there is a medicinally important class of compounds, related to β -phenylethylamine, that are called sympathomimetic drugs (because they stimulate the sympathetic nervous system) or pressor drugs (because they cause an increase in blood pressure).

Examples of these compounds are found in the three classes of amines, i.e., primary, secondary and tertiary. All, however, can be considered as derivatives of β -phenylethylamine (see Tables 25 and 26).

The β -phenylethylamine structure may be altered in four major ways:



1. Phenolic hydroxyl substitution on the benzene ring.
2. Substitutions on the beta carbon atom.
3. Substitutions on the alpha carbon atom.
4. Substitutions on the amino group.

PROPERTIES OF PRESSOR AMINES

The physical and chemical properties of these amines are typical of amines (Chapter 10) and parallel very closely those of the basic esters having local anesthetic action (see Chapter 15). The free amines generally occur as oil-like liquids or solids of low melting point. Some possess an asymmetric

carbon atom and are, therefore, optically active. A few are used in pharmacy as the free amines and these are cases where the volatility of the amine is necessary, as in "inhalers," or where the amine is in an oily solution for local (nasal) or intramuscular injection. The amines are insoluble or slightly soluble in water but they are soluble in organic solvents, fats or oils.

Salt formation with organic or mineral acids is the same as that explained in Chapters 10 and 15. Sulfuric and hydrochloric acids are the most popular because the salts are readily prepared, are stable and are easily water-soluble. These salts are all fine, white, crystalline powders, soluble in water but insoluble in oils or organic solvents. They may be employed in aqueous solution for topical application; some are used by injection.

Incompatibilities of the amine salts are encountered with any basic material and the alkaloidal reagents. The derivatives with aliphatic hydroxyl groups respond chemically as aliphatic alcohols, by esterification, acetylation and oxidation. The phenolic hydroxyls on the benzene ring react as do phenols and produce color reactions with ferric chloride.

Those containing a catechol (dihydroxybenzene derivatives) nucleus oxidize so easily in air or by traces of alkali, that an antioxidant is necessary. Sodium bisulfite is usually used, although even it presents the objections of being irritant and of producing a high acidity. Those compounds having a chain of three carbon atoms (propane derivatives) are usually quite stable.

THE MODE OF ACTION OF THE SYMPATHOMIMETIC AMINES

The peripheral effects of the sympathetic (adrenergic) nervous system are brought about by the release of the chemical mediator, sympathin, at the nerve endings and also by the release of epinephrine by the adrenal medulla. The sympathin and epinephrine, which are probably identical, act

upon a receptive mechanism of the muscles or glands to bring about the physiologic response. Some muscles or glands are stimulated while others are inhibited. Epinephrine is rapidly destroyed in the body by certain enzyme systems and, therefore, the effects of injected epinephrine or sympathetic nerve stimulation are very transient.

The sympathomimetic amines (substances related chemically to epinephrine) probably act upon the receptive mechanism in a manner similar to epinephrine. The more closely related the amines are to epinephrine, the more nearly similar their actions are to those of epinephrine. The theory that ephedrine and related substances act by protecting naturally occurring epinephrine from destruction by the enzyme amine oxidase is probably not true since there is good evidence to show that amine oxidase is not responsible for the *in vivo* inactivation of epinephrine.¹

Some of the sympathomimetic amines appear to have a greater affinity for the receptive mechanism than does epinephrine and, therefore, tend to block out and diminish the effects of epinephrine.

AMINES

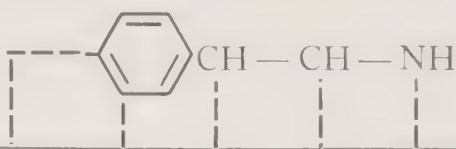
Compounds related to β -phenylethylamine have been of prime interest to pharmaceutical chemists since the elucidation of the structure of epinephrine in 1897. Due to the developments in synthetic chemistry, there are available new compounds that possess specific characteristics, so that one can select a compound that is useful in such conditions as those involving the respiratory system, the eye, the gastro-intestinal system, metabolism, the central nervous system, the vasomotor system or the heart.

Table 25 (page 221) shows the structural relationships of the primary pressor amines.

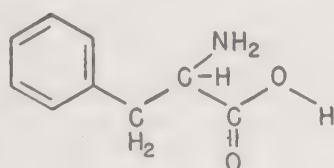
PRIMARY AMINES

Phenylethylamine (β -Phenylethylamine). This amine occurs during the decay

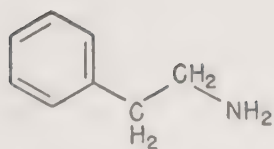
TABLE 25. STRUCTURAL RELATIONSHIPS OF THE PRIMARY PRESSOR AMINES

	ACTIVITY OF EPINEPHRINE As (1)						DURATION
MONAMINES							
β-phenylethylamine	1/183	H	H	H	H	H	Short
Tyramine	1/70 to 1/100	HO	H	H	H	H	Short
Hydroxytyramine	1/30 to 1/40	HO	HO	H	H	H	
β-phenyl-β- hydroxy-ethylamine	1/142	H	H	HO	H	H	Short
Amphetamine	1/225	H	H	H	CH ₃	H	Long
Dexedrine	1/190	H	H	H	CH ₃	H	Long
Propadrine	1/60	H	H	HO	CH ₃	H	Long
Paredrine	1/50 to 1/100	HO	H	H	CH ₃	H	Long
β- <i>p</i> -hydroxyphenyl-β- -hydroxy-α-methyl-ethylamine	1/53	HO	H	HO	CH ₃	H	
Arterenol	1/2-1.5	HO	HO	HO	H	H	Short
Ethylnorepinephrine		HO	HO	HO	CH ₂ CH ₃	H	

of proteins (meat) by the decarboxylation of the amino acid, phenylalanine.



Phenylalanine

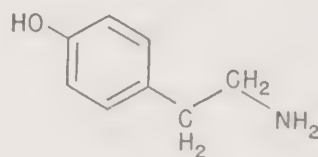


β-Phenylethylamine

It also may be prepared synthetically by several methods. The free amine is an oily liquid, but it does form a white, crystalline hydrochloride. It has only a slight pressor activity and is not used in medicine. β-Phenylethylamine is of greater interest from a theoretical point of view than for any therapeutic usefulness. Its basic structure represents the simplest compound possessing a sympathomimetic activity, an activity that the lower members (phenylamine or aniline,

phenylmethylaniline or benzylamine) do not share. The pressor action is slightly stronger than that of *l*-ephedrine, but it is of much shorter duration. This fact, along with its inactivity on oral administration, has discouraged its use in medicine.

Tyramine (*p*-Hydroxyphenylethylamine, Systogene, Uteramine). Tyramine occurs naturally in ergot and also is obtained by the putrefaction of proteins and by decarboxylation or heating tyrosine.



Tyramine

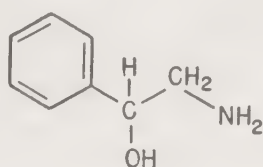
It readily is prepared by the reduction of *p*-hydroxybenzylcyanide (HOC₆H₅CH₂CN), forming a hydrochloride and a phosphate that are crystalline, white and water-soluble.

In systemic effect it resembles epinephrine but is about 1/100 as potent. Although once used, it has been superseded by better compounds. As a local hemostatic it has no value. The salt may be taken orally or ad-

ministered hypodermically in doses of 20 to 40 mg.

Closely related but inactive arylamines are hordenine (β -*p*-hydroxyphenylethyldimethylamine) and mescaline (β -3,4,5, trimethoxyphenylethylamine).

Beta-phenyl- β -hydroxyethylamine (Phenylethanolamine). This compound, an isomer of tyramine, has the hydroxyl on the beta carbon atom of the chain. It does have an action similar to ephedrine and is 1/350

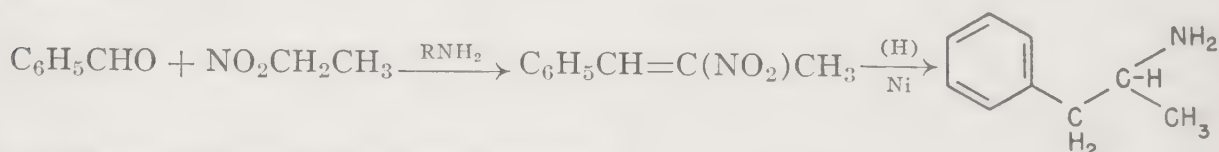


β -Phenyl- β -hydroxyethylamine

as active as epinephrine, although it cannot be administered orally.

In this compound, methyl substitution on the amine reduces the pressor activity by half.

Amphetamine N.N.R. (Benzedrine, Racemic Amphetamine, Racemic desoxynorphedrine, 1-phenyl-2-aminopropane). Amphetamine is a racemic mixture prepared by several methods, of which the following is typical:

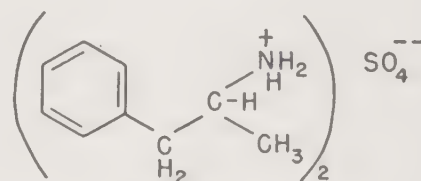


It occurs as a colorless, oil-like liquid having a strong basic odor and a burning taste.

The free base is volatile, as is the carbonate, and it readily forms salts with acids. The absence of hydroxyl groups is thought to be responsible for the volatility of the amine. In air it is rapidly converted to the carbonate. In the form of the free amine or carbonate, it is used by inhalation (Benzedrine Inhaler N.N.R.) to shrink the nasal mucosa, thereby relieving congestion and itching in most cases. Oil solutions can also be used. This use is similar to the local application of ephedrine. The salts of amphetamine also

will produce similar activity on topical application but are rarely so employed.

Amphetamine Sulfate N.N.R. (Benzedrine Sulfate). This is a white crystalline salt having the characteristic properties of amine salts. A solution containing 1 Gm. in 10 cc. has a pH between 5.0 and 6.0. It is the racemic form having good pressor action but rather poor analeptic activity and it is used orally. Oral administration is possible with the propane derivatives (See propadrine, ephedrine, etc.) but not with the ethane derivatives (See epinephrine). It, like ephedrine, is useful in the treatment of narcolepsy, by producing insomnia. Because of the stimulating action on the central nervous system, it is used in the treatment of certain depressive conditions such as those associated with apathy and psychomotor retardation. Its use to avert sleepiness and to reduce weight are to be condemned.



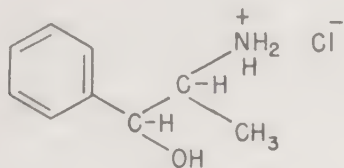
Amphetamine Sulfate

The average dose is 2.5 to 10 mg.

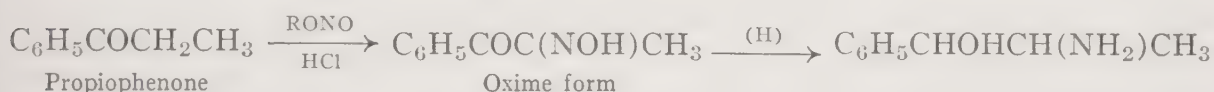
Dexedrine Sulfate (*d*-Amphetamine Sulfate, *d*-Benzedrine Sulfate). Dexedrine sulfate is the dextro isomer of Amphetamine Sulfate N.N.R. The levo form has been found to possess good pressor action, rather poor analeptic activity. In contrast to this, the dextro form (dexedrine sulfate) has slight pressor action and good analeptic properties. The use, therefore, is for those conditions requiring central nervous system stimulation.

The average dose is 5 mg.

Phenylpropanolamine Hydrochloride (Propadrine Hydrochloride) N.N.R. (Norephedrine Hydrochloride, *dl*-1-Phenyl-1-hydroxy-2-aminopropane Hydrochloride).



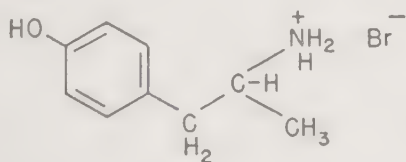
Propadrine is available in the racemic form and may be prepared from propiophenone.



The hydrochloride has an odor like that of benzoic acid and has the usual appearance and solubilities. An aqueous solution is neutral to litmus. A comparison of the formula with that of ephedrine shows a lack of the methyl group (CH_3) on the amine, altering the action by making it more prolonged and constrictive than that of ephedrine, less effective on the central nervous system and less toxic. It is used locally and internally as is ephedrine.

Average Dose: 1 per cent solution; 0.66 per cent jelly; 24 mg. orally.

Paredrine Hydrobromide (*p*-Hydroxyphenyl-2-aminopropane Hydrobromide).



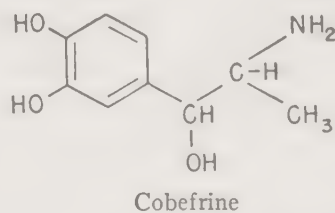
Paredrine is an isomer of propadrine, having the hydroxyl not on the alkyl chain but in the para position on the phenyl group. Note also that it may be considered as derived from tyramine with the alkyl extended to propane. It is prepared synthetically and possesses the aforementioned properties of amine salts.

This compound is an effective sympathomimetic amine, stable and of rapid

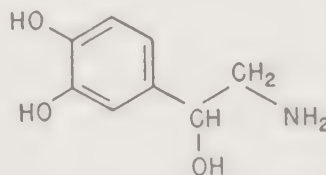
sustained action. There is practically no anxiety effect. Besides being used as a nasal decongestant, it has a good mydriatic action that does not affect accommodation. A 1 per cent solution is usually employed. Solutions made tear-isotonic with boric acid and suspensions with sulfathiazole are also used.

Cobefrine (Norhomo-Epinephrine, Corbasil, Iso-Adrenaline) is prepared similarly to norephedrine and is used in the form of the hydrochloride in aqueous solution. The

amine is isomeric with epinephrine and has its characteristic activity on the circulation. It is a strong vasoconstrictor and may replace epinephrine for use with local anesthetics. In surgical shock it is useful as an analeptic. The hydrochloride is best suited for aqueous solution. It is superior to epinephrine in some responses and does not exhibit the harmful after-effects usually produced by epinephrine.



Arterenol (Nor-Adrenalin, *d*-3,4-Dihydroxyphenyl- β -aminoethanol).



The hydrochloride of racemic Arterenol is the one usually used. Oddly, Arterenol is the modification of the epinephrine molecule with the methyl group removed from the amine, thus producing a greater activity on

the heart than is exhibited by epinephrine. It is used in medicine as is epinephrine, although it has good, but weaker, vasomotor action, as well as bronchi-dilating effects.

Ethylnorepinephrine [Ethyl-norsuprarenin, E.N.E., E.N.S., Butanefrine, *dl*-1-(3,4-Dihydroxyphenyl)-2-amino-1-butanol]. This recently introduced pressor agent,² has a chain of four carbon atoms. It is one-fifth as toxic as epinephrine, with little pressor activity. Without appreciable increase in blood pressure, it relaxes the bronchial muscles. There is promise for it in the treatment of asthma and some cardiac conditions since patients who are no longer benefited by epinephrine will respond to butanefrine.

group in the beta position is known to reduce the toxicity of a compound. There is very little irritation, slight local tissue reaction and no stimulation of cardiovascular or central nervous systems. Each Vonedrine Inhaler N.N.R. contains 250 mg.

Ephedrine U.S.P. is an alkaloid obtained from species of *Ephedra* or produced synthetically. The drug Ma Huang, containing ephedrine, was known to the Chinese in 2800 B. C. and the active principle ephedrine was isolated by Yamanaski in 1885. Another Japanese worker, Nagai, obtained the pure alkaloid and named it ephedrine. Interest in the compound developed after the investigation of Chen in 1923, and the chem-

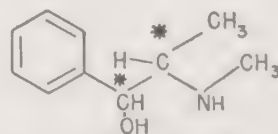
TABLE 26. STRUCTURAL RELATIONSHIPS OF THE SECONDARY AND TERTIARY PRESSOR AMINES

		ACTIVITY OF EPINEPHRINE AS (1) DURATION							
SECONDARY AMINES									
Vonedrine		H	H	CH ₃	H	H	CH ₃	Long	
Ephedrine	$l = 1/142$	H	H	HO	CH ₃	H	CH ₃	Long	
Suprifen		HO	H	HO	CH ₃	H	CH ₃		
Desoxycphedrine	$l = 1/550$ $d = 1/800$	H	H	H	CH ₃	H	CH ₃	Long	
Paredrinol		HO	H	H	CH ₃	H	CH ₃	Long	
Synephrine	$1/230$ to $1/470$	HO	H	HO	H	H	CH ₃	Short	
Phenylephrine	$1/9$	H	HO	HO	H	H	CH ₃	Short	
Epinephrine	1	HO	HO	HO	H	H	CH ₃	Short	
Isuprel	2 to 5	HO	HO	HO	H	H	<i>iso</i> C ₃ H ₇	Long	
Kephine		HO	HO	O	H	H	CH ₃	Short	
Epinine	$1/10$	HO	HO	H	H	H	CH ₃	Long	
TERTIARY AMINES									
Nethamine		H	H	HO	CH ₃	CH ₃	C ₂ H ₅	Long	
Bephedin		H	H	HO	CH ₃	CH ₃	CH ₂ C ₆ H ₅		
α -3,4-dihydroxyphenyl- α -hydroxyethylisopropylamine		HO	HO	HO	CH ₃	H	CH(CH ₃) ₂	Inactive	

SECONDARY AMINES

Phenylpropylmethylamine (Vonedrine, Racemic β -Phenyl-*n*-propylmethylamine) N.N.R. The free amine is a colorless to pale yellow liquid. This base is volatile and thus effective by inhalation, causing constriction of the nasal mucosa. The action is of long duration. The introduction of a methyl

ical synthesis was accomplished in 1929. The synthetic product is racemic and is known as ephetonin.



Ephedrine

This alkaloid is readily isolated from the Ephedra plant with alcohol or with benzene which has been made alkaline with calcium hydroxide or sodium carbonate. Impure ephedrine, obtained by evaporating the organic solvent, is dissolved in dilute hydrochloric acid and decolorized, and the solution is made alkaline and again extracted with organic solvent. By careful evaporation of the organic solvent at low temperature, fairly pure ephedrine is obtained.

Ephedrine has two asymmetric carbon atoms(*), which means that there are four optically active forms and two racemic, or *dl* forms. Racemic ephedrine (ephedrin) is in the N.N.R. as Racephedrine N.N.R., Racephedrine Hydrochloride N.N.R. and Racephedrine Sulfate N.N.R.; all of these forms are used as ephedrine herein described. Table 27 shows the relative pressor activity.

TABLE 27. RELATIVE PRESSOR ACTIVITY OF ISOMERS OF EPHEDRINE

ISOMER	RELATIVE PRESSOR ACTIVITY
<i>l</i> -Ephedrine	36
<i>dl</i> -Ephedrine	26
<i>d</i> -Ephedrine	11
<i>d</i> -Pseudoephedrine	7
<i>dl</i> -Pseudoephedrine	4
<i>l</i> -Pseudoephedrine	1

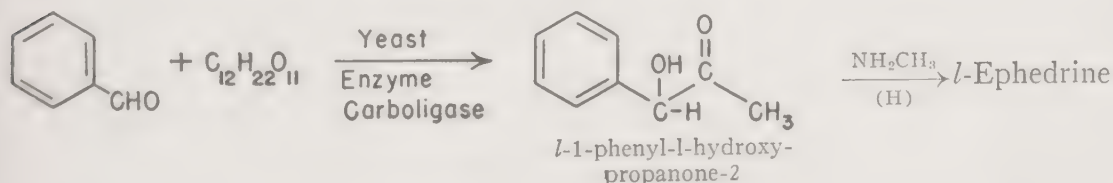
Natural ephedrine is *l*-ephedrine and, of the six forms, has the greatest pressor activity. The synthesis of the *l*-form is unique in that a fermentation process produces the essential intermediate *l*-1-phenyl-1-hydroxypropanone-2.

novel solubility properties since it is soluble in water (about 1 per cent), alcohol, some organic solvents or in liquid petrolatum. To prevent cloudiness, the anhydrous form should be used in oils. When left exposed, it will volatilize, especially at slightly above room temperature.

Ephedrine has physiologic effects very similar to those of epinephrine, although they are of longer duration and there is a more pronounced stimulation of the central nervous system. An outstanding advantage is that it may be given orally. Its chemical structure has a propane chain, in contrast to an ethane chain in epinephrine. After a comprehensive study of a series of compounds, it was concluded that the added methyl group of ephedrine confers oral activity. In this regard, note that β -phenylethylamine is inactive on oral administration, whereas amphetamine, having a methyl group on the alpha-carbon atom, is effective by mouth. Another important difference is the lack of hydroxyls on the phenyl group in ephedrine.

Ephedrine and its salts are used orally, intravenously, intramuscularly and topically, in a variety of conditions such as allergic disorders, colds, hypotensive states and narcolepsy. It is employed locally to constrict the nasal mucosa, to dilate the pupil or the bronchi and to diminish hyperemia. It is incompatible with sodium sulfathiazole and so they cannot be used together.

Some investigations indicate that ephedrine has the disadvantage in nasal therapy



The alkaloid is unstable in light and usually occurs as white crystals or granules that may contain not more than one-half molecule of water of hydration or be anhydrous. It has

of causing a secondary relaxation of the vascular layer of the submucous tissue, with resultant sluggishness of the turbinates.

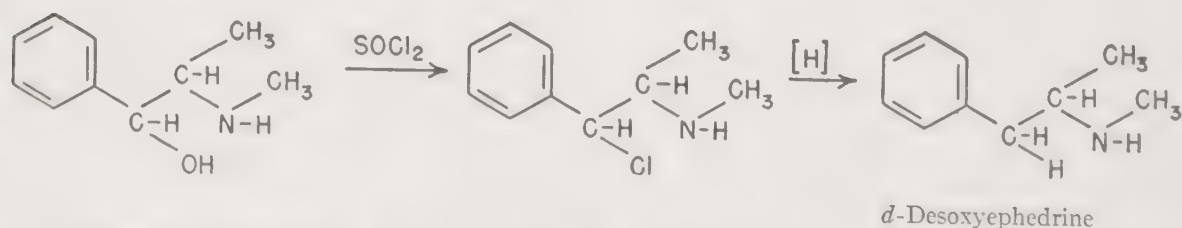
Systemically, it is effective for asthma,

hay fever, urticaria, low blood pressure and muscle weakness of myasthenia gravis.

Average dose: Local application—0.5 to 2 per cent solution; ophthalmologic application—4 per cent solution; orally—20 to 50 mg.

OFFICIAL OCCURRENCE	PER CENT EPHEDRINE
U.S.P.	
Ephedrine Hydrochloride	...
Ephedrine Sulfate	...
N.F.	
Ephedrine Hydrochloride Tablets..	...
Ephedrine Spray	1.0
Compound Ephedrine Spray.....	1.0
Ephedrine Sulfate and Phenobarbital Capsules	...
Ephedrine Sulfate Capsules.....	...
Ephedrine Sulfate Jelly.....	1.0
Ephedrine Sulfate Solution.....	3.0
Ephedrine Sulfate Syrup.....	0.4

Methamphetamine Hydrochloride³ (*d* Desoxyephedrine Hydrochloride, N-Methyl-Benzedrine, Methyl Benzedrine, Methyl Amphetamine, N-Methyl Phenylisopropylamine) N.N.R. is a synthetic progeny of ephedrine in which the hydroxyl group, replaced by a hydrogen atom, is attached to the carbon atom adjacent to the benzene ring. See the structure of benzedrine for further comparison. This structure may exist in a *levo*, *dextro* or racemic form. The names for each are: *levo*, Methyl Isonym; *dextro*, Norodin Methedrine, Desoxyn, D-O-E, Semoxydrin, Drenalfa and Pervitin; *racemic*, Oxydrine and Desamine. A synthesis from *l*-ephedrine involves halogenation and subsequent reduction.



It forms salts and has the physical and chemical properties of ephedrine.

A considerable amount is known regarding the use of the *d*-isomer. This form is similar in action to amphetamine sulfate but is more potent, of longer duration and has a more

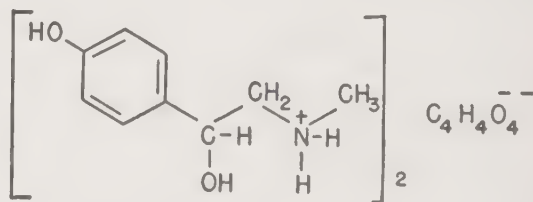
rapid onset. It increases the urge to work, increases energy and efficiency, elevates mood and counteracts sleepiness. The hydrochloride is used orally in the treatment of narcolepsy and mild depression and as an adjunct to control obesity.⁴

Topical application to the nasal mucosa produces good vasoconstriction and it can be used in solution with the sodium salts of the sulfa drugs.⁵ Most of the other agents, such as ephedrine and Propadrine, decompose in alkaline solution. An added advantage over most other agents is that there is little rebound turgescence.

The *l*-isomer is the least active of the three forms. It and the racemic form offer no advantages over the *d*-isomer and thus are little used.

The average dose is 5 mg.

Synephrine Tartrate (Sympatol) is



marketed as the racemic tartrate and occurs as a white, crystalline salt having the usual properties of amine salts. It is nonhygroscopic and stable in acid solution. It differs from epinephrine chemically only in that it has one rather than two hydroxyl groups on the benzene ring. In cases where only one

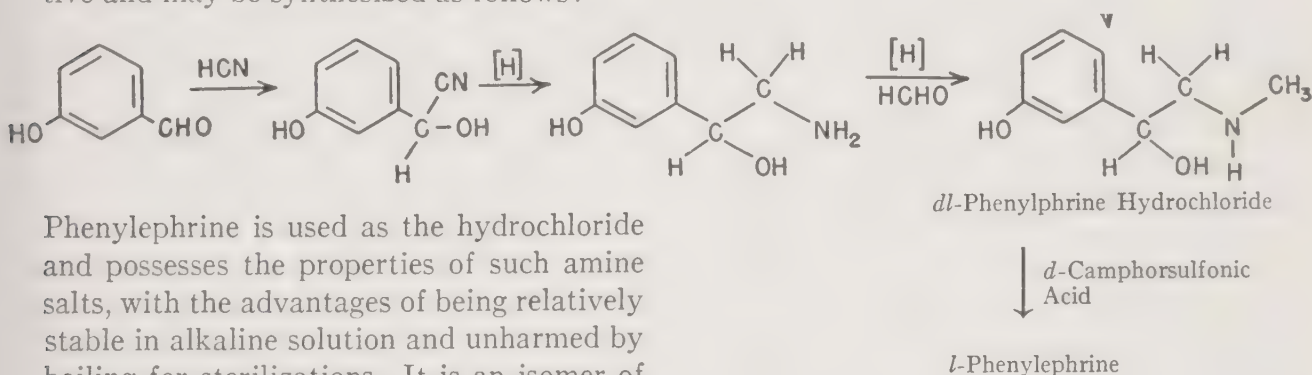
hydroxyl is present on the benzene ring, optimal activity is obtained when it is in the meta position. Therefore, Neo-Synephrine was developed. Orally, it is an effective sympathomimetic agent about 1/50

as active as epinephrine, producing peripheral circulatory stimulation with little or no effect on the central nervous system. On local application it is comparable to ephedrine and may replace epinephrine for use with local anesthetics.

It is used for chronic hypotension and mild collapse due to failing peripheral blood flow.

The average dose is 0.1 Gm.

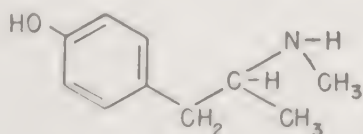
Phenylephrine Hydrochloride N.N.R. (Neo-Synephrine) is the salt of an isomer of β -3-hydroxyphenyl- β -hydroxyethylmethylamine. This is an unusual compound because it is a *m*-hydroxyphenylethylamine derivative and may be synthesized as follows:



Phenylephrine is used as the hydrochloride and possesses the properties of such amine salts, with the advantages of being relatively stable in alkaline solution and unharmed by boiling for sterilizations. It is an isomer of synephrine, but is much more active, having about one-fifth of the pressor activity of epinephrine and ten times that of synephrine. This compound is a vasoconstrictor and, on oral administration, is an active vasopressor. Applied locally, it is useful, like ephedrine, to constrict the blood vessels on mucous membranes. For certain conditions a solution of it is used as a mydriatic. There is available a nasal preparation composed of Neo-synephrine, as the free amine, and sulfathiazole.

The average dose on topical application is 0.25 per cent solution.

Paredrenol (*p*-hydroxyphenylisopropylmethylamine, Veritol, Pholedrine) is iso-



meric with ephedrine and is similar in action. It has been used as a stimulant in

circulatory failure, but there is a question as to its efficiency.⁶

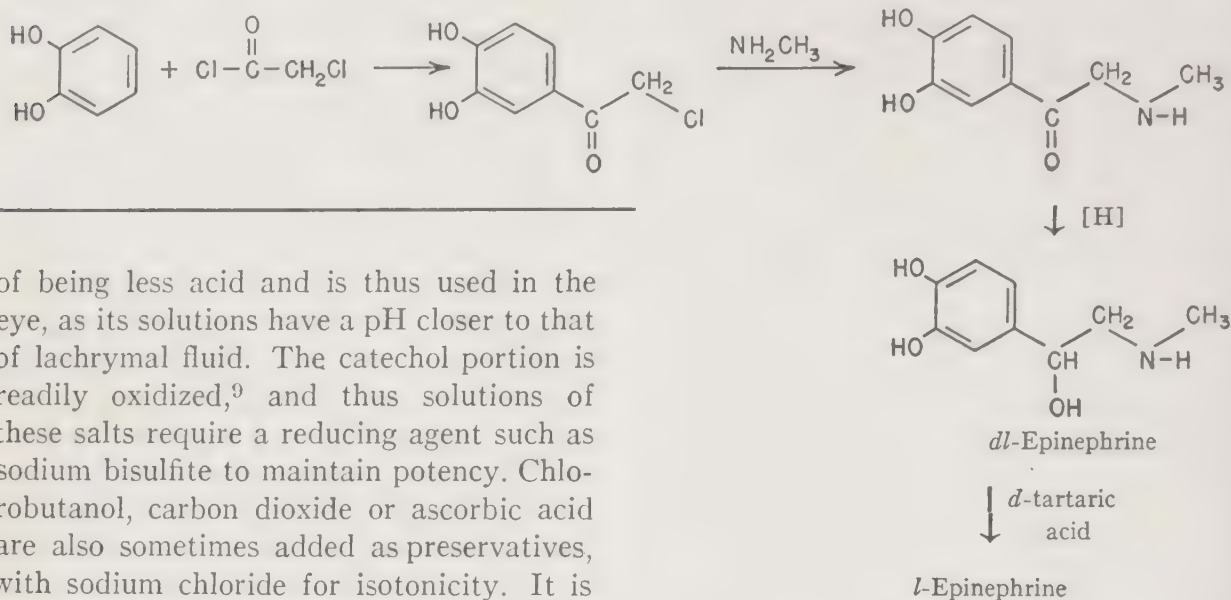
Epinephrine U.S.P. (Adrenalin, Suprarenalin, Suprarenin). Epinephrinelike activity was observed in extracts of adrenal medulla in 1895, and the factor was isolated by Abel and Crawford in 1897.

Jowet, in 1904, elucidated the structure and epinephrine was synthesized in 1905 by Stolz.

It is produced commercially by extracting suprarenal glands with warm, dilute hydrochloric acid. Air is excluded during the process. The extract is clarified with alcohol, concentrated in a vacuum, made alkaline

with ammonia and extracted with ether. A hydrochloride may be prepared with gaseous hydrogen chloride or the free amine obtained by evaporating the ether to dryness. Several methods of synthesis are available; the synthesis at the top of page 228 is an example.

The synthesis results in a racemic form that is about one-half as active physiologically as the levo form. Racemic epinephrine has been studied⁷ and several attempts have been made to introduce it.⁸ The dextro form is practically inactive. Epinephrine, as the free amine, is a white or brownish, crystalline, odorless powder. Due to oxidation, it slowly darkens on exposure to air. In this form it is available in oil solution for intramuscular injection and in glycerin solution for inhalation. Like the other amines, it forms salts with acids; for example, those now used are the hydrochloride, borate and bitartrate. The tartrate has the advantage



of being less acid and is thus used in the eye, as its solutions have a pH closer to that of lachrymal fluid. The catechol portion is readily oxidized,⁹ and thus solutions of these salts require a reducing agent such as sodium bisulfite to maintain potency. Chlorobutanol, carbon dioxide or ascorbic acid are also sometimes added as preservatives, with sodium chloride for isotonicity. It is destroyed readily in alkaline solution, in air, by weak oxidizing agents and by aldehydes.

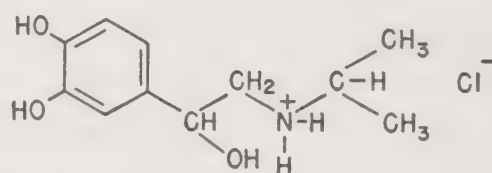
Local application is limited, but it is of value as a constrictor in hemorrhage or nasal congestion. Its use with local anesthetics has been pointed out, and as an inhalant, it is widely used to relax the bronchi in asthmatic conditions. Systemic administration is made in a variety of conditions such as asthmatic paroxysms, serum sickness, acute circulatory collapse and anaphylaxis where a vasoconstrictor is required. Forms of administration are aqueous or oil solutions, ointments and suppositories.

Epinephrine has the disadvantages of short duration of activity, decomposition of its salts in solution, vasoconstrictive action frequently followed by vasodilation and inactivity on oral administration.

The average dose intramuscularly is 0.06 to 1.0 cc. of (1 in 1,000).

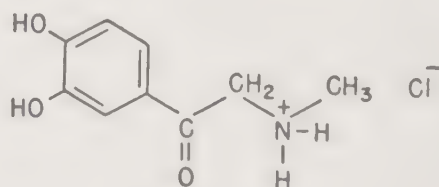
OFFICIAL OCCURRENCE U.S.P.	PER CENT EPINEPHRINE
Epinephrine Inhalation	1.0
Epinephrine Injection	...
Epinephrine Solution	0.1

Isuprel (Aludrin, Isopropyl Epinephrine, 3,4 - Dihydroxyphenyl - β - isopropylaminoethanol Hydrochloride).



The structure of Aludrin differs from that of epinephrine in having an isopropyl group attached to the amino nitrogen. It has superior bronchospasmolytic activity and appears to be useful in bronchial asthma. An advantage is that the blood pressure is not raised, but is lowered, due to dilation of the peripheral vessels. It may be given in very low concentration intravenously and is useful subcutaneously, sublingually, orally and by inhalation.

Kephrine Hydrochloride [(*l-m-p*-Dihydroxyphenyl)-1-keto-2-methylaminoethane Hydrochloride].

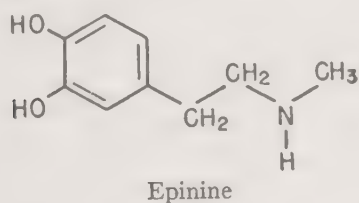


Kephrine is a structure of interest in the pressor class and has a keto group in the beta position where epinephrine has a hydroxyl

group. It is used locally to arrest bleeding by vasoconstrictive action on capillary vessels. It is less active than epinephrine, effective for one to two hours, and is not absorbed, thus has no effect on blood pressure.

Pharmaceutical application is in dusting powders, suppositories and impregnated bandages for the control of local bleeding.

Epine (3,4-Dihydroxyphenylethylmeth-ylamine) is marketed as the free amine and as the hydrochloride, both being more stable than epinephrine. Epine is a modification of the phenylethylamine structure and is one-tenth as active as epinephrine, which differs only in having a beta-hydroxyl group. In slightly acid solutions it is stable and may be sterilized by boiling.



The compound possesses strong vaso-motor and bronchidilation effects.

RELATIONSHIP BETWEEN STRUCTURE AND PHYSIOLOGIC ACTIVITY¹

1. Sympathomimetic activity is closely associated with compounds having a benzene nucleus separated from an amino nitrogen by two carbon atoms—(AR—C—C—N).

2. In general, the secondary amine type of compound is more toxic and less active than is the corresponding primary amine.

3. It appears that those compounds having a chain of three carbon atoms are more stable than are those containing a chain of two carbon atoms.

4. The structures containing dihydroxy-benzene are all unstable.

5. The properties of ephedrine, as distinguished from epinephrine, are believed to be caused by the presence of a third carbon atom in the chain and the absence of hydroxyl groups on the benzene ring. Ephedrine, in contrast to epinephrine, is effective

orally, has greater stability and is effective on the central nervous system.

6. The effect of the alcoholic hydroxyl at the beta position is variable; it may increase activity or decrease toxicity or do both.

7. The manner by which an increase in the length of a side chain alters the properties of a pressor agent is explained by the change of beta carbon atoms from primary to secondary. When the amino nitrogen is attached to a primary carbon atom (epinephrine), the enzyme, amine oxidase, readily deaminates the compound. The deamination is much slower when the amino nitrogen is attached to a secondary carbon (ephedrine).

8. $\text{AR}-\text{C}-\underset{\text{N}}{\text{C}}-\text{C}-$ A structure of this

type retains pressor activity, possesses oral activity and has an effect of long duration.

9. $\text{AR}-\text{C}-\underset{\text{N}}{\text{C}}-\text{C}-\text{C}-$ The pressor ac-

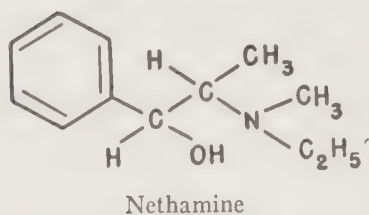
tivity can be expected to decrease and toxicity may increase as the length of the carbon chain increases.

10. Alkylation of the amino nitrogen to form a secondary amine tends to decrease activity and to increase toxicity.

11. Usually, substitution of hydroxyl in the phenyl group increases activity and alters toxicity. Mono-hydroxyl substitution is most effective in the following order: meta, para and ortho. Dihydroxy-substitution is best in 3,4-position.

TERTIARY AMINES

Nethamine Hydrochloride (*l*-N-Ethyl Ephedrine, Methylethylaminophenylpropanol Hydrochloride) is a stable hydrochloride, freely soluble in water or alcohol. It has activity like that of ephedrine and the same physical and chemical characteristics. It may be used under similar conditions. There are slight vasopressor or central nervous system effects, but it is a good relaxant of smooth muscle.

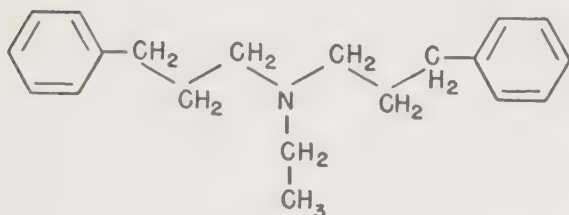


The average dose is 40 mg.

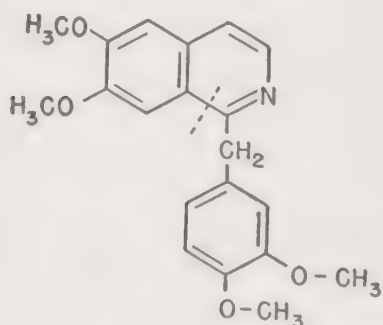
Bephedin (Benzylephedrine) is a relaxant of smooth muscle, having similar properties to those of ephedrine with about five times the antispasmodic activity but possessing fewer of the undesirable side-effects. Benzylephedrine, unlike ephedrine, does not increase blood pressure and has no effect on the heart in therapeutic doses. It is used in the symptomatic treatment of bronchial asthma.

The average dose is 30 mg.

Sestrone (*Bis-γ-Phenylpropylethylamine*).

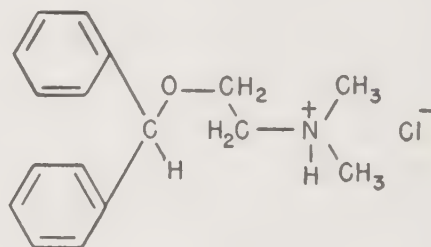


In the search for a neurotropic type of spasmolytic, amine compounds related to the alkaloid papaverine were studied. Although several were used clinically, none have become very popular in therapeutics. If the isoquinoline ring of the papaverine formula is opened at the dotted line, it is revealed that a derivative of di- β -phenylethylamine results.

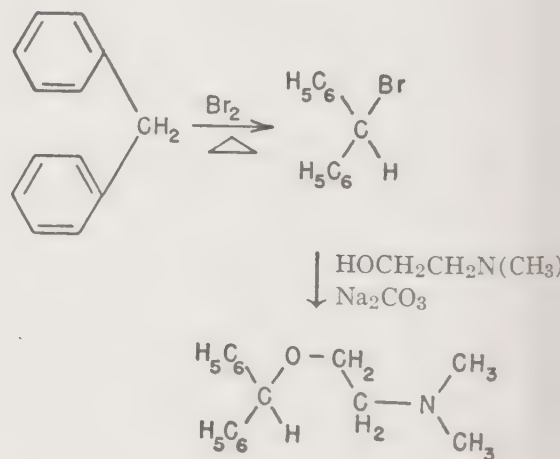


There have been many studies¹⁰ to develop tertiary amine compounds along this line of approach. Sestrone is an example of a successful compound having about 2.3 times the activity of papaverine. Cyverine, an amine very similar to Sestrone, has cyclohexyl groups in place of the phenyl groups; it, too, is an effective spasmolytic.

Diphenylhydramine Hydrochloride (**Benadryl Hydrochloride**) N.N.R., (β -dimethylaminoethyl Benzhydrylether Hydrochloride) is a synthetic tertiary amine possessing both antiallergic and antispasmodic



activity. A synthesis may be carried out by starting with diphenylmethane as follows:



It is available as the hydrochloride, which is a stable, white, crystalline powder soluble in water or alcohol and having a bitter taste. A 1 per cent aqueous solution has a pH of about 5.

This compound is an example of an anti-spasmodic¹¹ type of drug that seems to be specific in overcoming the pharmacological effects of histamine.¹² As an antihistamine¹³

agent, it is recommended in various allergic conditions and, to a lesser extent, as a spasmolytic.

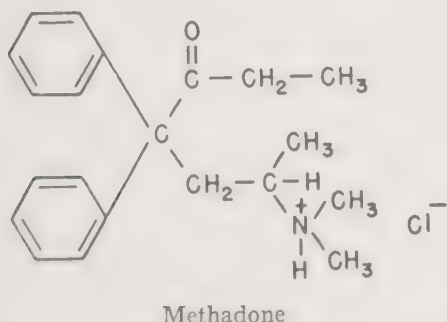
In antihistamine effect it is 650 times as active as papaverine and 15 to 30 times more active than aminophylline. It is useful either orally or intravenously in the treatment of urticaria, hay fever, bronchial asthma, drug allergy, vasomotor rhinitis and some kinds of dermatoses. The most common side effect is drowsiness. In the treatment of "colds" it is finding some use as a constituent of cough mixtures.

The average dose is 50 mg.

Mode of Action

The mode of action of antihistamine compounds may be considered as a competition, in tissue for a receptive substance, between the antihistamine agent and histamine. The combining of the antihistamine compound with the receptive substance at the site of action prevents histamine from exerting its characteristic effect on the tissue.

Methadone¹⁵ (Methadon, Amidon, Amidone, Dolophine, 10820 Adanon, AN-148) N.N.R. is racemic 4-4-diphenyl-6-dimethyl-aminoheptanone-3 hydrochloride, occurring as a white, crystalline material¹⁶ with a bitter taste, soluble in alcohol or water (5 per cent) but insoluble in ether.



The analgesic effect, and other morphinelike properties, are exhibited chiefly by the *l*-form. Aqueous solutions are stable and may be sterilized by heat for intramuscular and intravenous use. Like all amine salts, it is incompatible with alkali and salts of heavy

metals. It is somewhat irritating when injected subcutaneously.

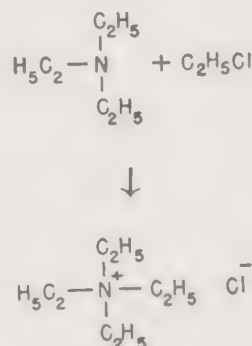
The toxicity of Amidone is three to ten times greater than morphine, but its analgesic effect is twice that of morphine and ten times that of isonipecaine (Demerol). It has been placed under federal narcotic control because of the morphinelike properties.

Methadone is a most effective analgesic, used to alleviate many types of pain. It can replace morphine for withdrawal symptoms and its addictive property is questionable. It produces less sedation and narcosis than does morphine and appears to have fewer side reactions in bedridden patients. In spasm of the urinary bladder and in the suppression of the cough reflex, Methadone is especially valuable.

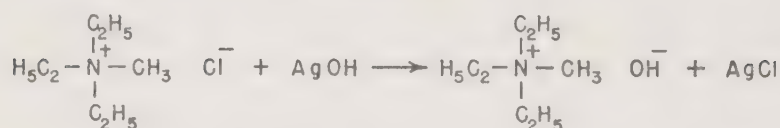
The average dose is 2 to 10 mg.

QUATERNARY AMINES

Quaternary amines, tetra-alkyl-ammonium salts, may be considered as completely alkylated ammonium salts. These salts are formed by adding a substance like an alkyl halide or alkyl sulfate to a tertiary amine. The result is a solid ionic substance that is soluble in water and insoluble in ether. Note the similarity of this reaction to that of tertiary amines with a mineral acid.



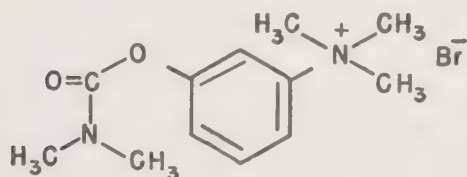
These salts are extremely stable and, unlike amine hydrochlorides, do not release the free amine upon treatment with an alkali; instead, they form a strong base. This amine base may be isolated by using silver hydroxide in its preparation.



Quaternary amines are more important pharmaceutically in the aliphatic compounds (see Chapter 10) than they are in the aromatic series. Recent studies have been made on these amines, in relation to their usefulness as antiseptics and wetting-agents (see Chapter 22).

The following compounds that are parasympathomimetic agents have been introduced as substitutes for physostigmine.

Neostigmine Bromide U.S.P. (Prostigmine Bromide, dimethylcarbamic ester of 3-hydroxyphenyl-trimethylammonium bromide).



This is a synthetic alkaloid developed in 1931.¹⁷ It is thought to contain the fundamental chemical structure of physostigmine that is responsible for the physiologic action.

This structure, $\text{CH}_3-\overset{\text{R}}{\underset{\text{O}}{\overset{|}{\text{N}}}}-\overset{\text{O}}{\overset{||}{\text{C}}}-\text{OH}$, a methylalkyl carbamic acid, when in ester linkage with a hydroxyphenyl containing a strongly basic group, *m*-hydroxyphenyldialkylamine (*m*- $\text{HOC}_6\text{H}_4\text{NR}_2$), possesses anticholinesterase activity.²⁰

A method of preparation is from dimethylcarbamyl chloride and the potassium salt of 3-hydroxyphenyldimethylamine. Methyl bromide readily adds to the tertiary amine, forming the stable quaternary amine (see formula for neostigmine bromide). It occurs as an odorless, white, crystalline powder having a bitter taste. It is soluble in water (1:1) or alcohol. The crystals are much less hygroscopic than are those of

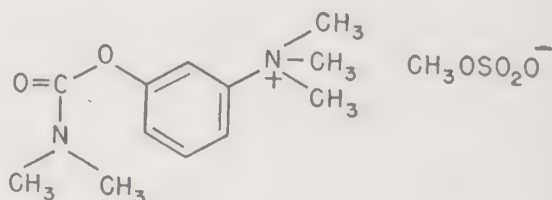
neostigmine methylsulfate and thus may be used in tablets. Solutions are stable and may be sterilized by boiling.

Prostigmine has a mechanism of action quite similar to that of physostigmine. The pharmacologic response is due to the inactivation of esterase, thus preventing the hydrolysis of acetylcholine. There may be a direct action of the drug on tissues innervated by cholinergic nerves, but this is not yet confirmed.

The uses of Prostigmine are similar to those of physostigmine, but they differ in having greater myotic activity, fewer and less unpleasant local and systemic manifestations and greater stability. Most frequent application is to prevent atony of the intestinal, skeletal and bladder musculature. A very important use is in the treatment of myasthenia gravis. The bromide is used orally.

The average dose is 15 to 30 mg.

Neostigmine Methylsulfate U. S. P. (Prostigmine methylsulfate, di-methylcarbamic ester of 3-hydroxyphenyl-trimethylammonium methylsulfate).



Neostigmine is prepared as in the method previously described for Prostigmine, and the quaternary amine is made with methylsulfate. It is an odorless, white crystalline powder with a bitter taste. Solutions of the amine are stable and can be sterilized by boiling. This increased stability is due to the meta substitution, as compared with para in physostigmine. The compound is too

hygroscopic for use in a solid form and thus is always used in injection.

The methylsulfate is used for the same conditions as the bromide. By subcutaneous or intramuscular injection it prevents post-operative distention.

The average dose is 0.5 mg.

OFFICIAL OCCURRENCE

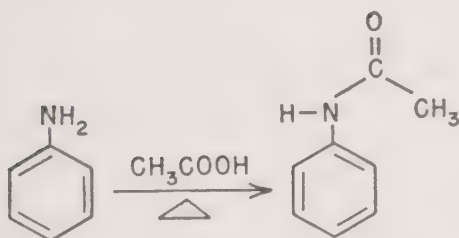
U.S.P.

Neostigmine Methylsulfate Injection

AMIDES

Amides of acids containing an aromatic group possess the same characteristics as aliphatic amides described in Chapter 10. Amide-type compounds are found in several pharmacologic classifications but most are important because of a sedative or analgesic property.

Acetanilid U.S.P. (Antifebrin, Phenylacetamid). Acetanilid is the monoacetyl derivative of aniline, prepared by heating aniline and acetic acid for several hours.



It is a member of the aniline group of analgesic-antipyretics commonly referred to as the "coal tar analgesics" because these drugs are prepared from aniline, a coal tar product. It can be recrystallized from hot water and occurs as a stable, white crystalline compound. It is slightly soluble in water (1:190) and easily soluble in hot water, acetone, chloroform, glycerin (1:5), alcohol (1:4) or ether (1:17).

Acetanilid is a neutral compound and will dissolve in neither acids nor alkalies, but by heating is hydrolyzed into its components, acetic acid and aniline. The acid hydrolysis is the quicker.

After sodium hydroxide saponification, the addition of a few drops of chloroform pro-

duces with the freed aniline poisonous phenylisocyanide. A number of color reactions are known for aniline, which is formed by boiling acetanilid with hydrochloric acid. Upon the addition of phenol to such a solution, a brownish-red color forms when a solution of sodium hypochlorite is added, changing to deep blue as ammonium T.S. is introduced. A violet color is produced when the acidified solution of acetanilid (aniline hydrochloride) is treated with a solution of sodium hypochlorite. Bromoacetanilid is formed when bromine T.S. is added to an aqueous solution of acetanilid.

It is prone to form eutectic mixtures with aspirin, antipyrine, chloral hydrate, menthol, phenol, pyrocatechin, resorcinol, salol, thymol or urethane. With certain agents, such as nitrous acid, spirit of ethyl nitrite, amyl nitrite and tincture of ferric chloride, acetanilid produces colors of red, green or yellow. If the solution can be made slightly alkaline, the formation of these colors may be prevented. In the presence of bromides and iodides, a precipitate is formed.

It is definitely toxic in that it destroys hemoglobin, affects the heart and may cause skin reactions and a jaundice condition.

Acetanilid is thought to exert its analgesic and antipyretic action by, first, being hydrolyzed to aniline and acetic acid, after which aniline is oxidized to *p*-aminophenol.¹⁸ This is then excreted in combination with glycuronic or sulfuric acid. The analgesic effect is selective on the nerve center responsible for most simple headaches and for the pain associated with many muscles and joints.

The average dose is 0.18 Gm.

OFFICIAL OCCURRENCE

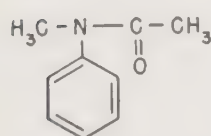
N.F.

Compound Acetanilid Powder 70.0

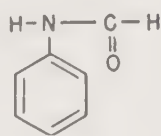
PER CENT
ACETANILID

A number of compounds related to acetanilid have been synthesized in attempts to find a better analgesic. They have not become very important in the practice of med-

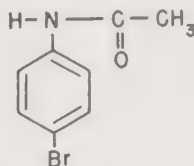
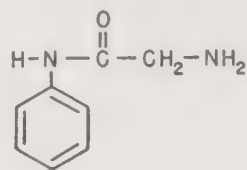
icine for they have little to offer over acetanilid. The physical and chemical properties are also much the same. Eutectic mixtures are formed with many of the same compounds.



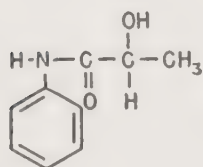
Exalgine



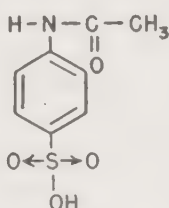
Formanilid

*p*-Bromoacetanilid

Glycocollanilid



Lactylanilid

*p*-Sulfonic Acid
Acetanilid

Formanilide is readily hydrolyzed and is toxic. The higher homologues of acetic acid are less soluble and, therefore, less active and less toxic.

Acetophenetidin (Phenacetin, Acetphenetidin) U.S.P. (Acetylphenetidin, Acetphen, Oxyethylacetamid). Acetophenetidin is acetanilid with the para hydrogen of the benzene ring substituted by the ethoxy group (C_2H_5O-).

Acetophenetidin is synthesized from phenol as is shown in the equations at the top of page 235.

It occurs as stable, white, odorless crystals having a slightly bitter taste. It is not very soluble in water (1:1,310), but is readily soluble in alcohol (1:15), chloroform (1:15) or ether (1:130).

In general properties and incompatibilities, such as being decomposed by acids and alkalies, it is similar to acetanilid. Various colors are formed with the same reagents, as mentioned for acetanilid.

The acetyl group is readily hydrolyzed by boiling with hydrochloric acid; upon addi-

tion of potassium dichromate, a ruby red color develops.

Iodine forms an insoluble compound (iodophenin), and eutectic mixtures are

formed with chloral hydrate, phenol, aminopyrine, pyrocatechin or pyrogallol.

Phenacetin is widely used as an analgesic and antipyretic, having essentially the same actions as acetanilid. It should be used with the same cautions since the toxic effects are the same as those of acetanilid.

The average dose is 0.3 Gm.

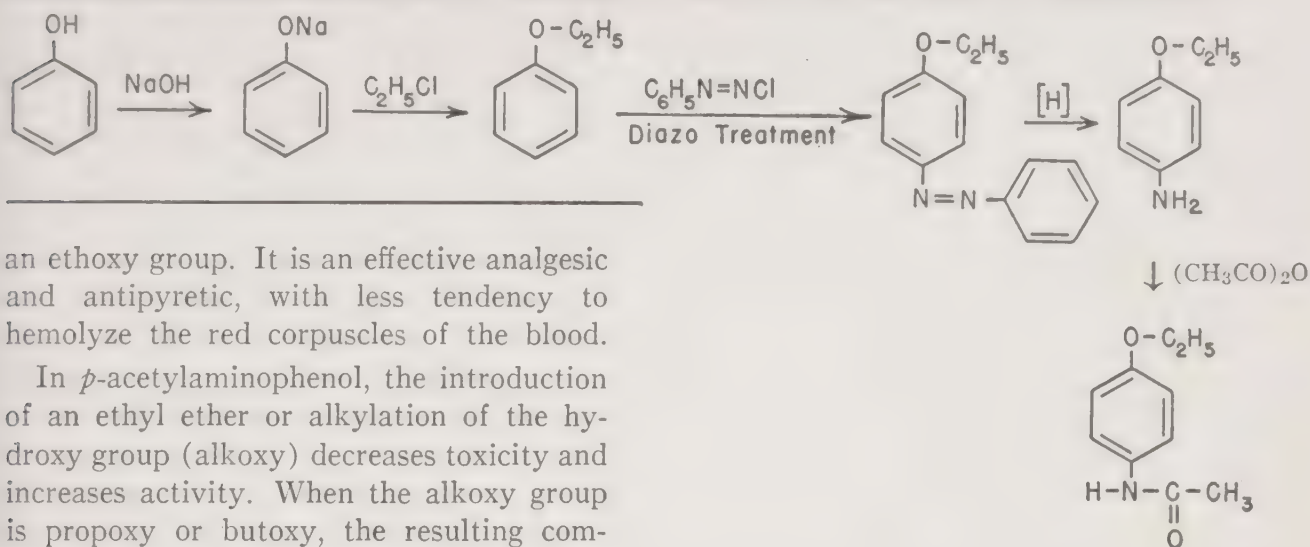
OFFICIAL OCCURRENCE

N.F.

Acetophenetidin and Phenyl Salicylate Tablets

In 1887, Duisberg started a study on derivatives of *p*-aminophenol. By this time acetanilid was in use and aniline was known to be converted into *p*-aminophenol in the body. The first step was the acetylation of *p*-aminophenol, which by analogy with acetanilid, might produce an active analgesic. The toxicity of *p*-acetylaminophenol is less than that of *p*-aminophenol and it does have some analgesic and antipyretic effect. However, it has a detrimental effect upon red corpuscles. Another approach was to attach an acyl group to both the *p*-hydroxyl and the amino groups. These compounds did have some activity, but it was of a low order. Finally, by replacing the hydroxyl group with an alkoxy group and an acyl group for a hydrogen of the amino group, a successful compound was obtained.

The simplest one is methacetin, $CH_3OC_6H_4NHCOCH_3$, the most effective of a series prepared. It, too, has a deleterious reaction on the red corpuscles. Acetophenetidin is the second compound of the series, having



an ethoxy group. It is an effective analgesic and antipyretic, with less tendency to hemolyze the red corpuscles of the blood.

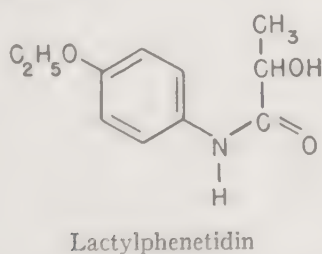
In *p*-acetaminophenol, the introduction of an ethyl ether or alkylation of the hydroxy group (alkoxy) decreases toxicity and increases activity. When the alkoxy group is propoxy or butoxy, the resulting compounds are either too toxic or the activity is greatly decreased.

There have been studied a series of compounds in which the hydrogen on the amino group of phenacetin has been replaced by an alkyl, e.g., $\text{C}_2\text{H}_5\text{OC}_6\text{H}_4\text{N}(\text{C}_2\text{H}_5)\text{COCH}_3$. Of the several compounds investigated, the ethyl derivative was found to be equal to, if not better than, acetophenetidin.

COAL TAR ANALGESICS RELATED TO ACETOPHENETIDIN

In an effort to produce a better analgesic than acetophenetidin, there have been synthesized several similar compounds in which the acetyl group is replaced by another radical.

Lactylphenetidin (Lactophenin) is prepared as is acetophenetidin, but lactic acid is used instead of the acetic acid. Thus, the compound resembles acetophenetidin except that the lactyl group occurs instead of the acetyl group.

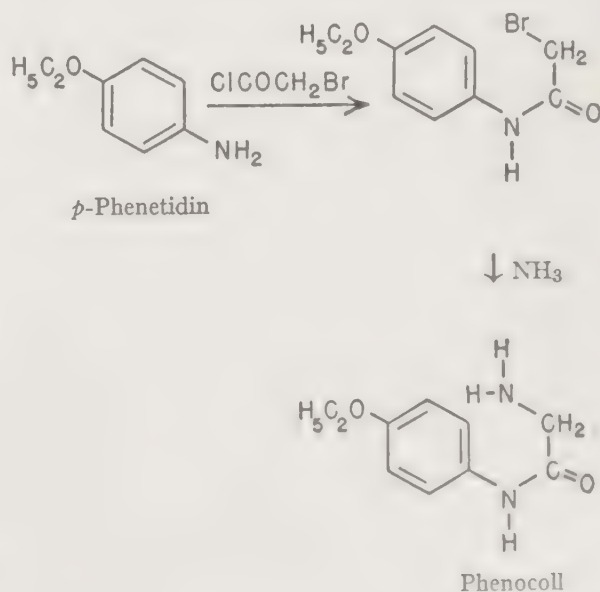


It is a white, crystalline powder, soluble in cold water (1:330) or alcohol (1:815).

Lactophenin, having no specific advantage, is used therapeutically as is acetophenetidin, in doses of from 0.32 to 1.3 Gm.

Other acids used to replace acetic acid in acetophenetidin have been salicylic and mandelic. In both cases the product is of no therapeutic importance.

Phenocoll (Aminophenacetin, Glycocoll-*p*-phenetidin, Phenamine). Phenocoll has an amino acid, glycine, in place of the acetic acid portion of acetophenetidin. This results in a compound soluble in water because it makes possible the formation of a hydrochloride salt at the amino nitrogen.



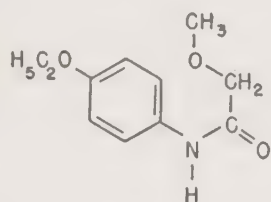
It is a white, crystalline powder, soluble in water or alcohol.

The average dose is 1.5 to 1.0 Gm.

Phenetsal is discussed in Chapter 15.

Kryofine (Methylglycolphenetidin, Methoxyacet-phenetidin, Kryofine.)

This compound has a hydrogen atom of the acetyl group in acetophenetidin replaced by a methoxy ($\text{CH}_3\text{O}-$) group:



Kryofine

It occurs as white crystals which are practically insoluble in water (1:600) and freely soluble in alcohol. The physical and chemical properties resemble those of acetophenetidin.

The average dose is 0.3 to 1.0 Gm.

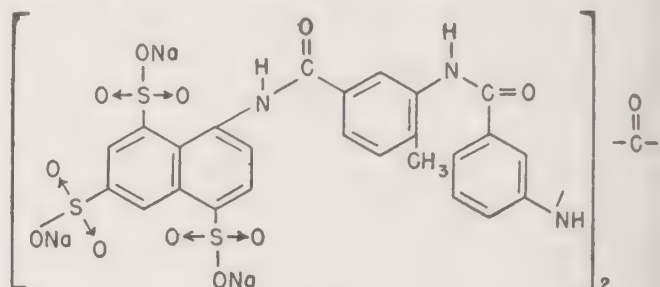
Salicylamide (*o*-Hydroxybenzamide) is a derivative of salicylic acid that has been known for over fifty years. It is readily prepared from salicyl chloride and ammonia. The compound occurs as a nearly tasteless, yellowish-white, crystalline powder. It is slightly soluble in water or alcohol. In alkaline solution with sodium carbonate or triethanolamine, decomposition takes place, resulting in a precipitate and a yellow to red color.

Salicylamide,¹⁹ exerts a moderately quicker and deeper depressing effect than does aspirin. Long studies on rats revealed no untoward symptomatic or physiologic reactions. There appears to be a difference in its metabolism from that of other salicylic compounds. In a comparative study²⁰ with common analgesics, salicylamide was found less toxic and more analgesic than aspirin.

POLYAMIDES

Suramin Sodium (Naphuride, Bayer 205) U.S.P. (Fourneau 309, Germanin, An-

trypol, Moranyl, Naganol) is an example of a complex urea derivative, chemically named bis(*m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-1-naphthylamino-4:6:8-sodium sulfate) carbamide. It has been used in the treatment of many thousands of cases of African sleeping sickness. It occurs as an odorless, white-to-slightly-pink, crystalline powder having a bitter taste; it is affected by light.



Suramin Sodium

The crystals are soluble in water, slightly soluble in alcohol and insoluble in organic solvent.

Toxic reactions are few in number, but if it is administered too rapidly, some side reactions such as pruritus, stomatitis and skin rashes may occur. Bayer 205 is an effective trypanosomicide in African sleeping sickness. When given in the first few weeks after the beginning of illness, there is a reasonable possibility of cure in infections due to *Trypanosoma rhodesiense*. A single intravenous injection of one gram will protect an individual from acquiring the disease for as long as three months, although he may be bitten by tsetse flies. It is used in the prophylaxis and treatment of trypanosomiasis.

The average dose is 1 Gm. intravenously.

S.U.P. 36 (Bis-*p*-benzoyl-*p*-aminobenzoyl-1-amino-8-naphthol-3:6-sodium sulfonate) was developed in England in 1936. It is intended for use as antibacterial in the treatment of influenza.

The average dose is 0.5 cc. intramuscularly.

S.U.P. 468 [Bis(*p*-benzoyl-*p*-aminobenzoyl-1-naphthylamine-4,6,8-sodium sulfonate) Carbamide]. S.U.P. 468 differs from S.U.P. 36 in the number and arrangement of the sulfonate groups. This has been found to

be an efficient antibacterial agent, particularly in streptococcal infections. It may be administered either intramuscularly or intravenously.

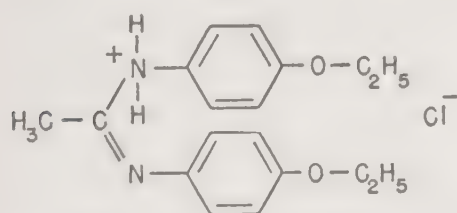
The average dose is 1 to 3 mg.

S.U.M. 36 [Bis(*m*-benzoyl-*m*-aminobenzoyl-1-amine-8-naphthol-3,6-sodium) sulfonate) Carbamide]. S.U.M. 36 is an English compound introduced as an antibacterial agent. It is recommended for use in the treatments of gonococcal infections.

The average dose is 0.002 Gm. intramuscularly.

AMIDINES

Phenacaine Hydrochloride U.S.P. (Holocaine Hydrochloride, Ethenyl Diethoxydiphenylamidine Hydrochloride) may be looked upon as an amidine of acetic acid (acetamidine). It may be synthesized from *p*-phenetidin and phenacetin. The hydrochloride occurs as odorless, white crystals having a slightly bitter taste and producing a numbness to the tongue. The crystals are stable in air, sparingly soluble in water (1:50), freely soluble in chloroform or alcohol and insoluble in ether. Aqueous solutions may be sterilized by boiling. The salt is very susceptible to decomposition by alkalies and has the same incompatibilities as the other local anesthetics (see Chapter 15).



Phenacaine Hydrochloride

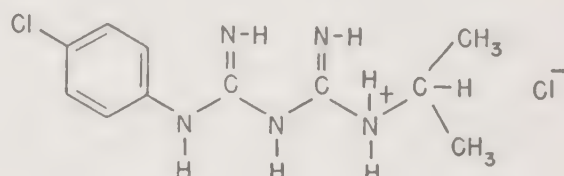
Phenacaine is more toxic than is cocaine and cannot be used for injection. However, it is a faster acting and more effective surface anesthetic, besides being nonmydriatic and not affecting accommodation. The solutions also possess some antibacterial properties.

It is very effective on mucous membrane but, due to toxicity, is used primarily in ophthalmology.

The average dose is in 1 per cent solutions and 1 to 2 per cent ointments.

GUANIDINE

Paludrine (Chlorguanide Hydrochloride, 4888, N₁-*p*-chlorophenyl-N₅-isopropylbiguanide hydrochloride).



Paludrine²¹ is an antimalarial drug developed in England. It has many advantages over atabrine and quinine. Some experiments have shown it to give complete prophylaxis and cure in some types of malaria. Paludrine is thought to exert its effectiveness by being converted in the body to another molecular form which is the active antimalarial agent. It is given orally in doses of from 12 to 700 mg.; few side effects are observed.

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17

Sulfur Compounds

MERCAPTANS, THIOLS

THIOETHERS, SULFIDES

SULFONES, SULFONIC ACIDS, THIOUREA
DERIVATIVES

SULFONAMIDES

PRODUCTS

SULFONES

PHOSPHORUS COMPOUNDS

A number of classes of organic compounds containing sulfur are known. The importance of sulfur compounds in biochemistry and pharmaceutical chemistry is becoming more evident as research in these fields progresses. A large number of enzymes,¹ including papain, urease, esterase, lipase, carboxylase, pyruvate oxidase, alcohol oxidase and choline oxidase, are known to depend on the presence of sulfhydryl (—SH , also called thiol) groups for their activity. Sulfur-containing amino acids are essential constituents of the diet if normal growth and bodily functions are to be maintained. Some vitamins, for example, biotin and thiamine, contain sulfur. A large number of the sulfur compounds have received wide application as chemotherapeutic agents, and the importance of the class can be expected to increase. Sulfur compounds occur abundantly in petroleum, coal tar and shale oil. In many cases the sulfur compounds are undesirable in the fin-

ished products such as gasoline and lubricating oils because of their tendency to produce acids resulting in excessive corrosion. The compounds are removed in various ways. As new uses are found for the sulfur compounds, they can be expected to assume more and more commercial importance.

Sulfur is in the sixth group of the periodic table, just below oxygen. Both atoms have six valence electrons and both form stable compounds in which the atoms have a valence of two. Sulfur also forms stable compounds in which the valence is four or six. Oxygen has some tendency to form compounds in which it exhibits a valence of four, consisting of three bonds and a plus charge, as indicated by various oxonium compounds

such as $\begin{array}{c} \text{H} \\ | \\ \text{O}^+ \\ / \quad \backslash \\ \text{H} \quad \text{H} \end{array}$, the $\begin{array}{c} + \\ \text{O} \\ // \end{array}$ structure

in flavones and xanthenes and the contributions from resonating forms such as

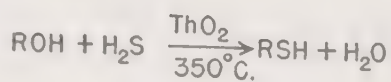
$\begin{array}{c} \bar{\text{O}} \\ | \\ \text{R}-\text{C}=\text{O}^+ \end{array} \begin{array}{c} \text{H} \\ / \end{array}$ to the structure of carboxylic acids. The difference between the behavior of sulfur and oxygen results from a number of factors. Oxygen is a first row element and hence only four orbitals are available for bond formation, limiting its bonds to four, while sulfur has additional orbitals available for bond formation. Oxygen has a maximum co-ordination number of four, while sulfur, being a second row element, has a maximum co-ordination number of six. Sulfur, like other second row elements, also has very little tendency to form double bonds,² while oxygen forms them quite readily. Sulfur does not have unpaired electrons and hence is not paramagnetic like oxygen, which has an unpaired electron which remains unpaired even in the oxygen molecule.

The divalent sulfur compounds are similar in some respects to the divalent oxygen compounds. However, the sulfur atom of thiols, which are also called mercaptans, and the sulfur in sulfides is easily oxidized to form stable compounds in which the sulfur has a valence of four or six. In general, all sulfur compounds in which sulfur exhibits a valence of either two or four are easily oxidized. The oxygen atom cannot be readily oxidized. Thiols may also form disulfides since the —S—S— linkage is reasonably stable. The —O—O— linkage is much less stable.

The more common types of sulfur compounds are shown in Table 28.

MERCAPTANS, THIOLS

The thiols may be synthesized by passing an alcohol and H_2S over hot thorium oxide,



by heating NaSH with a sodium alkyl sulfate in solution



TABLE 28. COMMON TYPES OF SULFUR COMPOUNDS

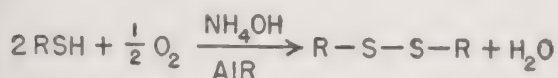
FORMULA	NAMES
$\text{R}-\text{S}-\text{H}$	Thiols, Thioalcohols, Mercaptans
$\text{R}-\text{S}-\text{R}$	Thioethers, Sulfides
$\text{R}-\text{S}-\text{S}-\text{R}$	Disulfides
$\begin{array}{c} \text{S} \\ \\ \text{R}-\text{C}-\text{H} \end{array}$	Thials, Thioaldehydes
$\begin{array}{c} \text{S} \\ \\ \text{R}-\text{C}-\text{R} \end{array}$	Thiones, Thioketones
$\text{Ar}-\text{S}-\text{H}$	Thiophenols
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{S}-\text{H} \end{array}$	Thiolic Acids
$\begin{array}{c} \text{S} \\ \\ \text{R}-\text{C}-\text{OH} \end{array}$	Thionic Acids
$\begin{array}{c} \text{S} \\ \\ \text{R}-\text{C}-\text{SH} \end{array}$	Thiolthionic Acids, Dithioacids
$\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{OH} \end{array}$	Sulfinic Acids
$\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{OH} \\ \downarrow \\ \text{O} \end{array}$	Sulfonic Acids
$\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{NH}_2 \\ \downarrow \\ \text{O} \end{array}$	Sulfonamides
$\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{R} \end{array}$	Sulfoxides
$\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{R} \\ \downarrow \\ \text{O} \end{array}$	Sulfones
$\text{R}-\text{S}-\text{C}\equiv\text{N}$	Thiocyanates
$\text{R}-\text{N}=\text{C}=\text{S}$	Isothiocyanates
$\begin{array}{c} \text{S} \\ \\ \text{R}-\text{O}-\text{C}-\text{SH} \end{array}$	Xanthates, Xanthogenates

and by treating an alkyl halide with concentrated KSH solution.



The mercaptans are more acidic than the corresponding alcohols; thus, they dissolve in basic solutions and react with the heavy metals to form mercaptides or thiolates. It is essentially this property which makes some of these compounds such as BAL an effective antidote for "Lewisite" and other heavy metal poisoning. Some of the mercury thiophenolates are also valuable antiseptics.

Mercaptans are easily oxidized to disulfides; in the presence of ammonium hydroxide, air brings about the conversion.



Reducing agents easily reverse the process. This oxidation-reduction system is of great importance biologically because it is involved in the conversion of cysteine to cystine and glutathione to oxidized glutathione.

Thiols, in spite of their greater molecular weight, have a lower boiling point than the corresponding alcohols; thus, methyl mercaptan boils at 7.6° C and methyl alcohol at 64.7° C. As one goes up the series, this difference decreases until the higher mercaptans containing over seven carbon atoms boil at almost the same point as the alcohols. This behavior is undoubtedly due to the fact that strong hydrogen bonds are present in alcohols but not in thiols. Hydrogen bonds or hydrogen bridges are structures in which hydrogen forms such a bridge or link between two other atoms. The bond has a strength of the order of 2—8 kilo. calories and is present when hydrogen is attached to strong electronegative atoms such as fluorine, oxygen or nitrogen. However, as the non-polar portion of the molecules becomes larger and larger, the relative size of the OH group to the rest of the molecule becomes proportionately smaller; so the attractive forces between the molecules due to the hydrogen bonds become sufficiently decreased to approximately equal the small effect due to the greater weight of the sulfur atom.

Methanethiol is a gas, the other aliphatic thiols being colorless liquids. Methanethiol is found in the urine after eating asparagus and it is produced sometimes in the intestines. The unpleasant odor associated with thiols is well known, and this property is made use of by gas companies to impart a characteristic odor to natural gas. The gas is passed over sulfur wastes from oil refineries or admixed with enough thiols to give it a distinct odor. Cases are known in which pipes carrying mercaptans have burst with the result that adjacent grocery stores have had to go out of business. Butanethiol or butyl mercaptan has been isolated from the secretion of skunks, and it has an odor characteristic of the skunk. Other thiols have garliclike odors. As the molecular weight of the compound increases, the unpleasant odor diminishes until the nonyl and decyl thiols have pleasant odors.

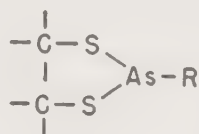
Mercaptans sometimes give rise to severe irritations when in contact with the skin, and inhalation of the vapors produces headache. Thiols have been used in the largest quantities as intermediates in the synthesis of various dyes.

Thioglycerol (Monothioglycerin, 3-Thio-2-hydroxy propanol). Thioglycerol, $\text{HSCH}_2\text{—CHOH—CH}_2\text{OH}$, is a liquid which decomposes before the boiling point is reached. It is miscible with alcohol and slightly soluble in water. A solution in glycerol, in water or in physiologic salt solution, 1:1,000, has been used to stimulate cell proliferation and promote granulation in sluggish wounds.

BAL (Dimercaprol, Dithioglycerol, 2,3-Dithio-1-propanol), $\text{CH}_2\text{SH—CHSH—CH}_2\text{OH}$, is a colorless liquid with a skunk-like odor. BAL is soluble in water (1:16). It was developed during World War II by the British³ as an antidote for "Lewisite." The name BAL is an abbreviation for British Anti-Lewisite. It is an effective antidote for poisoning with arsenic, gold, antimony, mercury, and perhaps other heavy metals. The

skin damage resulting from arsenical vesicant agents can be prevented by a previous application of BAL preparations. The damage to the skin by the same agents can also be arrested and perhaps reversed by application of BAL shortly after exposure. In systemic poisoning resulting from various arsenical agents, parenteral administration of BAL in oil has been demonstrated to be quite effective.

The antidote properties of BAL for the metals are associated with the fact that the heavy metal ions tie up the —SH groups in the tissues and thus interfere with the pyruvate oxidase and perhaps other enzyme systems which are dependent on the —SH group for their activity. The synthetic dithiol compounds such as BAL compete effectively with the tissues for the metal, removing the metal by forming a ring compound of the type



which is relatively nontoxic and is fairly rapidly excreted. To exhibit the detoxifying effect it is apparently necessary for the compound to have two thiol groups on adjacent carbon atoms so that a ring compound can be formed. Monothiol compounds are much less effective.

BAL has been applied locally as an ointment 5 per cent W/V in a base of lanolin, Lanette wax and diethylphthalate. It is injected intramuscularly as a 5 or 10 per cent solution in peanut oil to which 2 grams of benzyl benzoate is added for each gram of BAL to make the latter miscible with the peanut oil in all proportions. An N.N.R. product, 2,3-Dimercaptopropanol in oil, corresponds to this formula. Solutions of this type can be sterilized in nitrogen-filled ampules by heating to 170° C. for one hour without having more than 1.5 per cent of the

BAL destroyed in the process. Solutions of BAL in water or propylene glycol are reported to be unstable.

The dosage is 2.5 to 3 mg. per Kg., given at four hour intervals the first two days then at six hour intervals the third day and finally at twelve hour intervals until complete recovery. Toxic manifestations are usually noted if 5 mg. per Kg. are given.

BAL-Intrav (Dithioglycerolglucoside), the glycoside formed from BAL and glucose, is reported by British workers to be superior to BAL for treating systemic poisoning by injection. As might be expected, it has a much higher water solubility than BAL and is much less toxic, its L.D.₅₀ being about 7.5 Gm. per kilo. It can be given by intravenous injection, and the ring compound it forms with "Lewisite" has a very low toxicity. Systemic "Lewisite" poisoning is reported to be counteracted more effectively by this agent, and even advanced cases of poisoning in experimental animals have made a full recovery.

THIOETHERS, SULFIDES

These compounds are the sulfur analogues of ethers. They are named in a similar fashion, thus CH₃—S—CH₃ is methyl sulfide, dimethyl sulfide or methylthiomethane and C₂H₅—S—C₂H₅ is ethyl sulfide, diethyl sulfide or ethylthioethane. Mixed thioethers, such as CH₃—S—C₂H₅ which is ethyl methyl sulfide or methylthioethane, are known. Most of the thioethers, like the thiols, have disagreeable odors. Allyl sulfide, (CH₂=CH—CH₂)₂S, is the chief constituent in oil of garlic. The sulfides may be prepared by a modification of the Williamson synthesis of ethers.



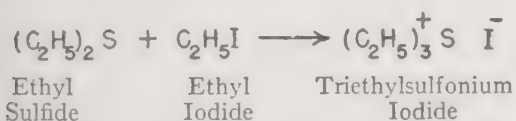
Another method involves saturating a solution of potassium sulfide with an alkyl halide and then distilling.



Since the thioethers do not have a hydrogen atom attached to sulfur, they have no acidic properties and, hence, do not undergo reactions with bases or metals. The most important reaction they undergo is oxidation,

first to a sulfoxide, $\text{R}-\overset{\text{O}}{\underset{\uparrow}{\text{S}}}-\text{R}$, and then to a sulfone, $\text{R}-\overset{\text{O}}{\underset{\uparrow}{\text{S}}}-\overset{\text{O}}{\underset{\downarrow}{\text{S}}}-\text{R}$. This reaction may be

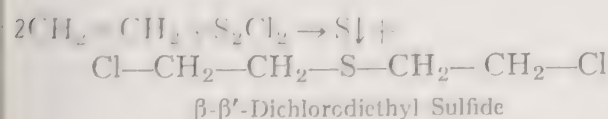
carried to the sulfoxide state by using 30 per cent hydrogen peroxide in acetic acid or it may be carried to the sulfone stage by using acid potassium permanganate in acetic acid solution. The thioethers differ markedly from ethers with respect to the above oxidation reactions. They also differ in respect to their reactions with alkyl halides. Thus, a thioether will react with an alkyl halide to produce a sulfonium salt. These compounds are soluble in water, and the solution conducts electricity.



These compounds are analogous to the quaternary ammonium halides in that they virtually are ionized completely, and the corresponding hydroxides are as strong bases as sodium hydroxide.

Divinyl sulfide, $(\text{CH}_2=\text{CH})_2\text{S}$, is found in the volatile oil obtained from *Allium ursimum*.

Mustard Gas (β,β' -Dichlorodiethyl sulfide, Yellow Cross) is actually a liquid which boils at 217°C . with slight decomposition. It is colorless, oily, and has a faint mustard-like odor. It is made by passing ethylene into sulfur monochloride.



The compound was one of the most effective war gases used in World War I. It is a vesicant having a blistering action on the skin, and in addition it has a very destructive effect on the air passages, lungs and eyes. One part in thirteen thousand is fatal if breathed for five minutes. It has been used experimentally in the treatment of cancer in animals and has been reported to induce mutations in *Drosophila melanogaster* as effectively as X-rays.

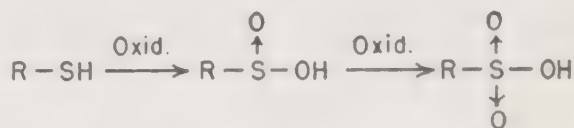
Disulfides are formed by mild oxidation of thiols or by heating the mercury salts of thiols.



Mitigal (Dimethylthianthrene, Dimethylbiphenylene Disulfide) is a yellow oil, insoluble in water but soluble in organic solvents, and probably consists principally of 2,6-dimethylthianthrene ($\text{CH}_3-\text{C}_6\text{H}_3-\text{S}_2-\text{C}_6\text{H}_3-\text{CH}_3$). It is used as an anti-pruritic in various skin diseases and as a parasiticide in scabies. It is applied as an ointment or in a solution of alcohol in castor oil, or it may be employed without a vehicle.

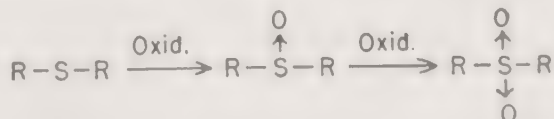
SULFONES, SULFONIC ACIDS, THIOUREA DERIVATIVES

Strong oxidizing agents convert mercaptans to sulfinic acids and sulfonic acids.



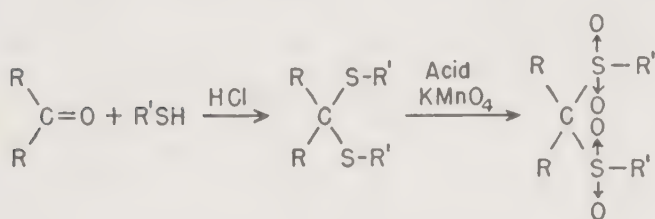
The sulfinic acids cannot be isolated because of their very rapid oxidation to sulfonic acids.

Thioethers are oxidized by nitric acid or an organic peroxide to sulfoxides and the latter, on oxidation by permanganate are converted to sulfones.

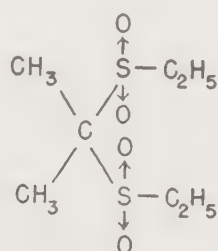


Compounds such as sulfonal and trional can be made by reacting a ketone with a

mercaptan, producing a mercaptal which is the sulfur analogue of an acetal. The mercaptal is then oxidized to the sulfone.



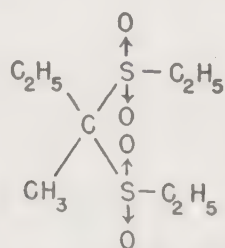
Sulfonmethane (Sulfonmethanum, Sulfonal) N.F. (Diethylsulfondimethylmethane).



Sulfonmethane

Sulfonmethane is a white, crystalline powder, soluble in water (1:365) and in alcohol (1:60). It was first introduced as a sedative in 1888. It is slowly excreted, and the sedative action is prolonged; this may lead to a cumulative effect with continued use. It is a very slow-acting unreliable anesthetic. The average dose is 0.75 Gm.

Sulfonethylmethane (Sulfonethylmethanum, Trional) N.F. (Diethylsulfonmethylmethane).



Sulfonethylmethane

Sulfonethylmethane is soluble in water (1:200) and in alcohol and ether. It is more active than sulfonmethane and is absorbed more rapidly and excreted with less tendency for cumulative effects. Sulfonmethane and sulfonethylmethane, when given in ex-

cessive doses, may cause hematuria to appear in the urine. At one time, the sulfonmethanes were widely used as hypnotics, but, at the present, they largely have been replaced by superior agents.

The average dose is 0.75 Gm.

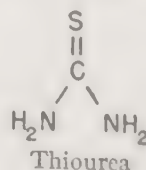
Methiodal Sodium (Skiodan) N.N.R. (Sodium Iodomethane Sulfonate). Methiodal Sodium, $\text{ICH}_2\text{SO}_3\text{Na}$, is a white, crystalline, odorless powder; it is soluble in water and slightly soluble in alcohol. It has a slight saline taste followed by a sweetish after-taste. It decomposes upon exposure to light, turning a yellow color. Both the solid compound and its water solutions should be kept protected from light.

It is used as a contrast medium in roentgenography. For intravenous urography, a dose of 2 Gm. for each fifteen pounds of body weight is administered in sterile aqueous solution containing from 20 to 40 Gm. per 100 cc.

Ichthammol (Ammonium Ichthosulfonate) N.F. (Ichthyol, Ichthynat, Isarol, Hirathiol). Ichthammol is a mixture of sulfur compounds in which the sulfur is present as sulfonates, sulfones or sulfides. It is made by sulfonating the distillate from certain bituminous schists and neutralizing the product with ammonia. The mixture of compounds before neutralization by the ammonia is collectively known as "sulfo-ichthyolic acid." Ichthammol has a high sulfur content and is a viscous dark-brown liquid with a strong empyreumatic odor. It is miscible with fats and soluble in water and glycerin.

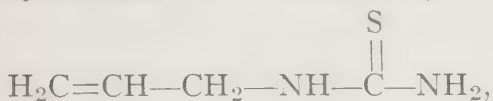
It is emollient and weakly antiseptic, and has been used in treating various skin disorders and to promote healing of inflammations. For these purposes it is usually applied as Ointment of Ichthammol N.F.

Thiourea N.N.R. (Thiocarbamide)



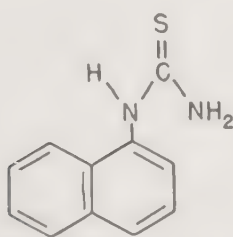
is a white solid. It can be made by heating ammonium thiocyanate or by the action of ammonia and hydrogen sulfide on cyanamide. Thiourea has properties as an antithyroid agent, although it is less effective in this respect than some of its derivatives. It is used as an antioxidant for epinephrine, to preserve the natural color of dried fruits, to protect wool and furs from textile pests, and as a sizing agent in the treatment of paper. It is also used as an intermediate in the synthesis of thiobarbiturates and thiouracil compounds.

Allylthiourea ("Thiosinamin"),



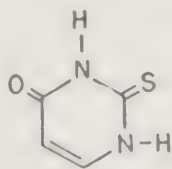
is claimed to have a softening action on certain animal tissues and has been used subcutaneously for the softening of fibrous scars. At the present time it is comparatively little used.

ANTU (α -Naphthylthiourea) has been employed as an effective rat poison against Norway rats. It is reported to be less efficacious against other types of rats.



α -Naphthylthiourea

Thiouracil (2-Thiouracil) is a colorless crystalline powder that has a bitter taste.

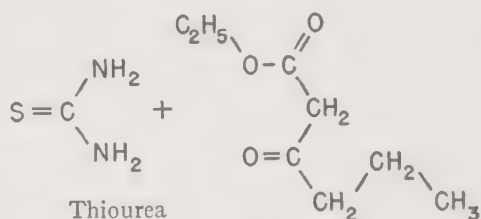


Thiouracil

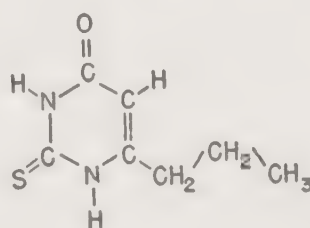
It is slightly soluble in alcohol, very slightly soluble in ether and water and virtually insoluble in benzene. It is used as an antithyroid drug because of its ability to

interfere with the formation of thyroxin or thyroglobulin. It is of some use in treating hyperthyroidism and thyrotoxicosis, particularly in cases where operation is contraindicated. Thiouracil therapy produces adverse reactions in a rather high percentage of patients. The complications include granulocytopenia, dermatitis, drug fever, leukopenia, jaundice and anemia. The initial dose is 0.4 Gm. per day, followed by 0.1 or 0.2 Gm. per day when the basal metabolic rate is within the normal range. Medication should be discontinued at once if adverse reactions are encountered.

Propylthiouracil N.N.R. (6-*n*-Propyl-2-thiouracil) is used in the treatment of hyperthyroidism. It is synthesized from thiourea and a β -keto ester.⁴



Ethyl β -Ketocaproate



6-*n*-Propyl-2-thiouracil

This particular derivative of thiouracil is more effective than thiouracil itself or any of a number of other compounds that have been tested for antithyroid activity.⁵ It is not a fundamental cure for hyperthyroidism but is supposed to inhibit the production of thyroglobulin. It is effective against the different types of hyperthyroidism, whether represented by nodular or diffuse goiter, but it has not been found to have any value in simple goiter.

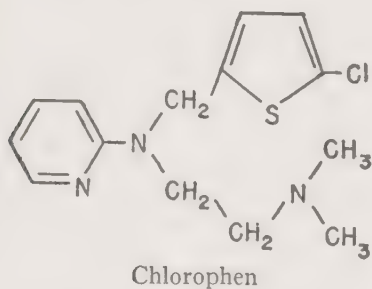
Excessive doses of propylthiouracil give rise to hypothyroidism, with symptoms such

as sluggishness, slowing of the pulse rate and dropsylike swelling.

Adverse reactions with propylthiouracil are much less frequent than they are with thiouracil. However, a certain percentage of untoward reactions are still encountered with the propyl derivative. These may include granulocytopenia and drug fever.

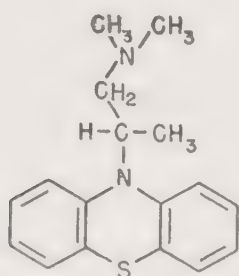
The dose varies from 150 mg. to about 25 mg. daily. The usual practice is to start with a comparatively high dose and then to adjust the maintenance dose by determining the basal metabolic rate.

Chlorophen (*N'*-Pyridyl-*N'*- α -chloro-thenyl-*N*-dimethylethylenediamine) and the corresponding bromine derivative, Bromophen, are similar in structure to tripelenamine, having an α -halogen thenyl group replacing the benzyl group in tripelenamine.



The compounds are antihistaminic agents and are being used at the present time.

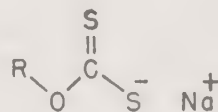
3277 RP [*N*-(β -Dimethylamino- α -methyl-ethyl)-phenothiazine] is an antihistaminic compound also in the stage of being evaluated.



Carbon Disulfide (Carbon Bisulfide), CS_2 , is synthesized from the elements at

high temperature. The commercial preparation is a colorless liquid with a strong, unpleasant odor. The odor is not objectionable in the highly purified compound. The compound is used in 10 Gm. doses sealed in gelatine capsules to destroy the larvae of the bot fly in horses. Carbon disulfide is inflammable and poisonous, the continued respiration of an atmosphere containing 1.5 mg. per liter causing death. It is used in industry as a solvent, as a chemical intermediate and as a rodenticide.

It combines with alcohols in the presence of alkali to form metal xanthates or xanthogenates.



Some of these are used in the flotation process for separating ores from the gangue. The xanthate formed with cellulose is water-soluble, and such a solution, known as viscose, is forced through spinarettes into a bath of dilute acid which hydrolyzes off the xanthate regenerating the cellulose. One form of rayon is produced in this way, as is cellophane, by forcing the viscose through a slit.

Sodium Thiocyanate (Sodium Sulfocyanate) **N. F.** (Sodium Rhodanate, Sodium Rhodanide). Sodium Thiocyanate, $\text{NaS}-\text{C}\equiv\text{N}$, is a white, odorless crystal with a salty taste. It is affected by light and is hygroscopic. It is very soluble in water (1:0.7) and is soluble in alcohol (1:4). It is precipitated by many alkaloids and by salts of copper, zinc, silver, lead and iron. It is used as a prophylactic and as a curative in the treatment of infections of Shiga bacillus. Its chief medical use is in the treatment of hypertension. Toxic reactions are fairly frequent, and it is necessary to measure blood levels to effectively control the dosage. The rate of excretion of the drug varies widely

in different patients. The thiocyanates are readily absorbed from the intestinal tract and distributed throughout the extracellular fluids. This property of the drug has been used to measure the volume of the extracellular fluids of the body, by noting how much these fluids dilute a given dose. The average dose is 0.3 Gm.

OFFICIAL OCCURRENCE	PER CENT SODIUM THIOCYANATE
N.F.	
Sodium Thiocyanate Elixir..	0.04

Potassium Thiocyanate (Potassium Sulfocyanate, Potassium Rhodanate) N.F., $K-S-C\equiv N$, is a colorless, odorless, compound that occurs in transparent, prismatic, hygroscopic crystals soluble in water (1:05) and in alcohol (1:12). The water solutions are neutral to litmus and impart a cooling, salty taste. The solutions are affected by light and should be stored in well-closed, light-resistant containers free from iron.

Potassium thiocyanate is used in the manufacture of certain drugs and in the detection of copper, silver, iron and certain alkaloids. It is employed therapeutically for the treatment of arteriosclerosis, high blood pressure and urinary calculi.

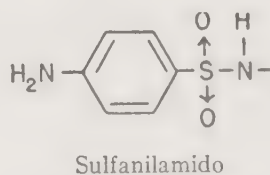
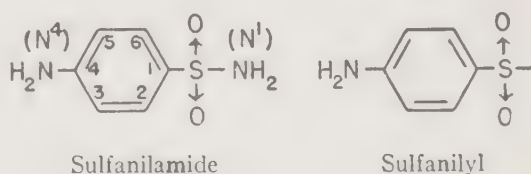
The average dose is 0.3 Gm.

Allyl Isothiocyanate, N.F. (Allyl Sulfocyanate, Volatile Oil of Mustard), $H_2C=CH-CH_2-N=C=S$, is a colorless oil with a very pungent, irritating odor and an acrid taste. It is miscible with alcohol and soluble to the extent of 0.2 Gm. in 100 cc. of water. Allyl isothiocyanate is made by reacting allyl iodide with a solution of potassium isothiocyanate. It is a powerful rubefacient. The dose is 0.008 cc., but it is rarely given internally. Allyl isothiocyanate is formed along with potassium hydrogen sulfate and glucose when the glycoside sinigrin, which is found in black mustard seed, is hydrolyzed.

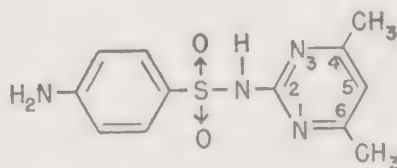
SULFONAMIDES

The discovery that *p*-aminobenzene sulfonamide is a good bacteriostatic agent was one of the most important developments in the history of chemotherapy. This compound, commonly called sulfanilamide since it is the amide of sulfanilic acid, was first made by Gelmo⁶ in 1908. It was not until 1932, however, when some azo dyes of sulfanilamide synthesized by Mietzsch and Klarer⁷ were later tested by Domagk⁸ and found to be effective bacteriostatic agents. The realization by Trefouel, Trefouel, Nitti and Bovet⁹ that it was the sulfanilamide portion of the azo dyes that was responsible for the activity started the synthesis of thousands of sulfanilamide derivatives and related compounds.

The atoms in sulfanilamide are numbered as follows:

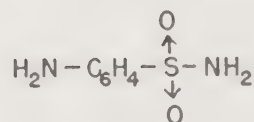
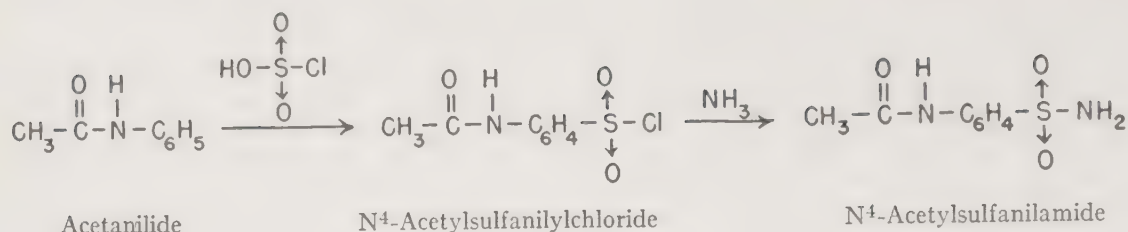


and the two radical names are formed in the usual way. In naming heterocyclic substituted sulfonamides the point of attachment of the hetero-ring is given.



N1-(4,6-Dimethyl-2-primidyl)-sulfanilamide,
Sulfamethazine

Sulfanilamide can be made as follows:



Sulfanilamide

The intermediate N⁴-acetylsulfanilylchloride has been used to synthesize over a thousand N¹ derivatives by reactions with compounds of the type R—NH₂ and

H
|
R—N—R'

followed by hydrolysis of the acetyl group. A large number of N⁴ derivatives have been prepared by reacting acyl chlorides or anhydrides with sulfanilamide and by other methods.

Some reactions for the preparation of N¹ and N⁴ sulfanilamide derivatives are shown at the top of page 249.

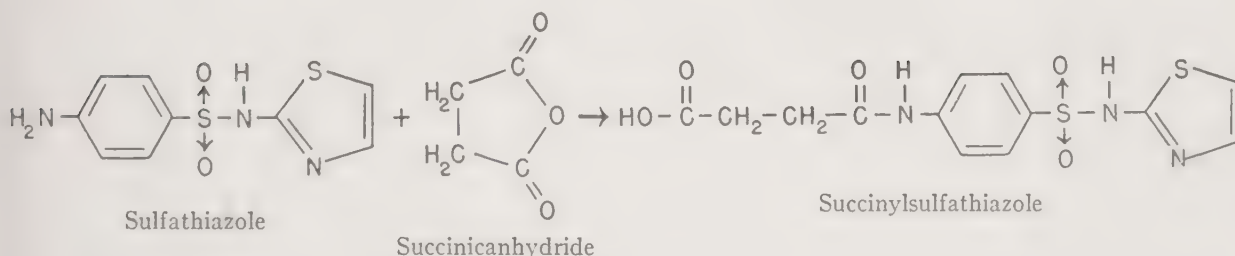
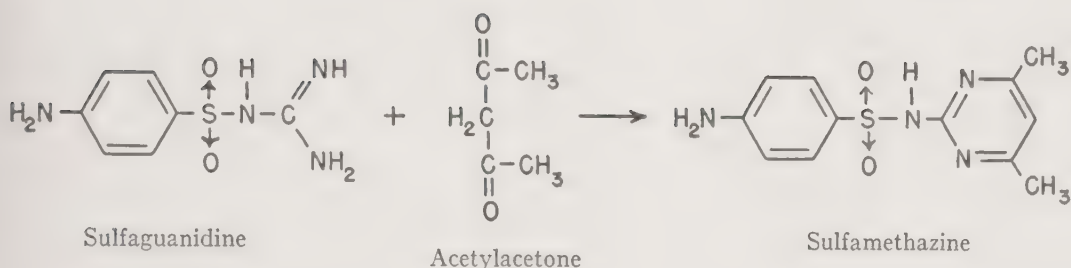
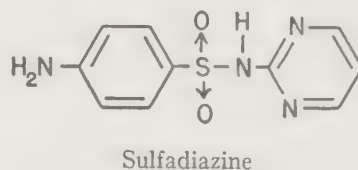
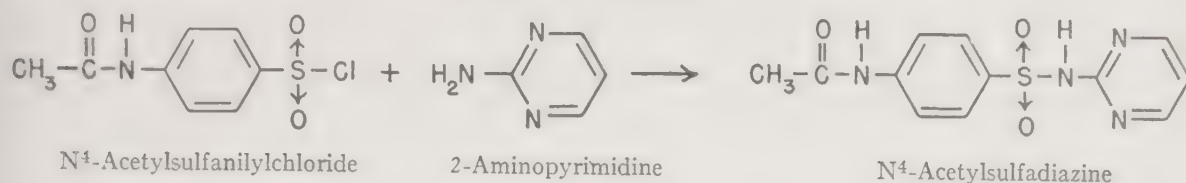
Woods¹⁰ and Fildes¹¹ suggested that sulfanilamide exerts its bacteriostatic action by competing with *p*-aminobenzoic acid (PAB). Subsequent studies have indicated that the sulfonamides produce their bacteriostasis by a competitive replacement of PAB in an enzyme system essential for the growth of susceptible organisms. Only those bacteriostatic substances antagonized by PAB are considered to possess a true sulfanilamide

The fact that no compound with a substituted aromatic amino group has been found to show sulfanilamide activity as such attests to the great importance of the free aromatic amino group for activity. All of the known N⁴-substituted compounds that are active in vivo break down in the body to produce the free aromatic amino group. Replacement of the aromatic amino (N⁴-amino) group with various other groups also destroys the activity. Changing the N⁴-amino group to other positions in the ring, giving orthanilamide and metanilamide, also results in inactive compounds. Substituents placed in the ring diminish the activity or completely de-

stroy it. The substitution of one of the hydrogens of the N¹-amino group with various groups results in a wide fluctuation in activity. This fluctuation has been correlated with the acid dissociation of the compound.¹⁰ The maximum activity is shown by those compounds having a pK_a of about 6.7, and the activity diminishes if the compounds are either more or less acidic. The reason for this behavior has been variously attributed to the negative character of the SO₂ group;¹² to the effect of the resonance, giving rise to flatness; to a separation of the charge, etc.;¹³ and to the ability of the compound to combine with proteins.¹⁴

The fact that 4,4'-diaminodiphenylsulfone does not dissociate as an acid and yet shows a high order of sulfanilamide activity is evidence which indicates that the presence of an acid group is not essential. Likewise, 4,4'-diaminobenzil shows an activity closely resembling that of sulfathiazole, both in quality and quantity of its antibacterial activity, indicating that neither an acid dissociation constant nor a sulfur atom is necessary for high activity. That the sulfur atom is not essential is also indicated by the antibacterial action of phosphanilic acid and *p*-aminobenzene phosphonous acid, both of which are antagonized by PAB.

The sulfonamides are effective agents against *Bacillus coli*, Friedlander's bacil-



lus, *Clostridium septicum*, *Clostridium welchii*, *Gonococcus*, *Meningococcus*, *Pneumococcus*, *Staphylococcus*, *Streptococcus hemolyticus* (beta), *Streptococcus viridans*, *Shigella dispar* and *H. influenza* infections.

The sulfonamides are not effective agents against most virus infections, although four diseases of probable virus origin, namely trachoma, molluscum contagiosum, lymphogranuloma venereum and follicular conjunctivitis, are reported to be affected by sulfonamide therapy. Anaerobic streptococci, the enterococcus group of streptococci and rheumatoid arthritis infections do not respond to the sulfonamides.

Table 29 (page 250) lists the sulfonamides and certain of their properties.

PRODUCTS

Sulfanilamide U.S.P. (*p*-Aminobenzene-sulfonamide) is an odorless, white, crystalline compound soluble in water (1:125) at 25° C. It is very soluble in hot water, hot alcohol, and in acids, bases, glycerin and acetone. It is insoluble in nonpolar organic solvents such as benzene, carbon tetrachloride, ether and chloroform.

A common method of assay is direct titration with a standard solution of sodium

TABLE 29. SULFONAMIDES

COMPOUND	CHEMICAL NAME	PROPRIETARY NAMES	pKa	APPROXIMATE pH - 10% SOLUTIONS SODIUM SALT	SOLUBILITIES IN 100 CC. OF WATER AT TEMPERATURE SHOWN
Sulfanilamide U.S.P.	<i>p</i> -Aminobenzene-sulfonamide	Prontylin Prontosil Album	10.43	12.3	1.7 Gm. 40° C.
N¹-SUBSTITUTED SULFONAMIDES					
Sulfacetamide	N ¹ -Acetyl-sulfanilamide	Sulamyd Albucid	5.38	9.7	
Sulfathiazole U.S.P.	2-Sulfanilamido-thiazole	M. & B. 760	6.48	10.2	94 mg. 37° C.
Sulfadiazine U.S.P.	2-Sulfanilamido-pyrimidine		7.12	10.6	12.3 mg. 37° C.
Sulfaguanidine U.S.P.	Sulfanilylguanidine monohydrate		...	...	190 mg. 37° C.
Sulfamerazine U.S.P.	2-Sulfanilamido-4-methyl-pyrimidine		7.06	10.5	31.8 mg. 32° C.
Sulfamethazine	4,6-Dimethyl-2-sulfanilamido-pyrimidine		7.37	10.7	
Sulfapyridine N.F.	2-Sulfanilamido-pyridine	Dagenan M. & B. 693	8.43	11.2	49.5 mg. 37° C.
Sulfapyrazine N.N.R.	2-Sulfanilamido-pyrazine		6.04	10.0	5.3 mg. 37° C.
Sulfathiadiazole	2-Sulfanilamido-1,3,4-thiadiazole		4.77	9.4	73 mg. 37° C.
N ¹ -Dimethylacroyl-sulfanilamide	N ¹ -3-Methyl-2-butenyl-sulfanilamide	Irgamid	...	8.3	
N⁴-SUBSTITUTED SULFONAMIDES					
Benzylsulfanilamide	N ⁴ -Benzyl-sulfanilamide	Septazine Proseptazine	...	...	
Succinylsulfathiazole U.S.P.	2-(N ⁴ -Succinyl-sulfanilamido)-thiazole	Sulfasuxidine	...	...	21 mg. 20° C.
Phthalylsulfathiazole	N ⁴ -Phthalyl-sulfathiazole	Sulfathalidine	...	...	
Sulfanilyl-sulfanilamide	N ⁴ -Sulfanilyl-sulfanilamide	Disulon Diseptal C	7.85	10.9	

nitrite. The aromatic amino group is diazotized, and the presence of excess sodium nitrite is detected with starch-iodide paper. Another method involves the diazotization of the aromatic amino group, followed by coupling with an aromatic amine such as β -amino-ethyl- α -naphthylamine [N-(1-naphthyl)-ethylenediamine], and finally, the colorimetric determination of the resulting azo dye. This method can be used for deter-

mining any of the N¹-substituted sulfonamides and the N⁴-substituted sulfonamides after hydrolysis, as well as sulfonilamide itself. It finds much use in determining the blood levels of these drugs.

Sulfanilamide has been used in the treatment of a wide variety of infections. In a number of cases, sulfanilamide is no longer the drug of choice, having been replaced by other sulfonamides or by other antibacterial

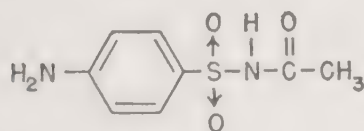
agents such as penicillin. In chancroid and actinomycosis, sulfanilamide may still be considered the drug of choice.

The dose depends on the severity and type of infection. The chief index for the control of therapy is the concentration of sulfanilamide in the blood or other body fluids and not the dose of the drug prescribed. In severe infections an initial dose of 0.1 Gm. per kilogram of body weight is sometimes given, followed by doses of one-sixth the initial amount at four hour intervals until the temperature remains normal for seventy-two hours.

Since the presence of small amounts of *p*-aminobenzoic acid inactivates the sulfonamides, the administration of local anesthetics¹⁵ such as procaine, butesin, butyn, benzocaine, etc., derived from this compound is contraindicated.

A number of toxic manifestations sometimes accompany use of this drug. These include central nervous system disturbances such as dizziness, vomiting, headache and nausea as well as drug fever, rashes, acidosis, cyanosis and hemolytic anemia. It is common practice to give sodium bicarbonate concurrently to prevent acidosis. The average dose is 2 Gm.

Sulfacetamide (*N*¹-Acetylsulfanilamide, *N*-Sulfanilylacetamide, Sulamyd, Sulfacet) is a white, crystalline powder. It is soluble in water (1:63 at 37° C.) and very soluble in hot water and in alcohol. This com-

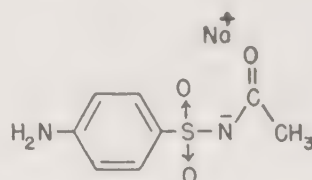


Sulfacetamide

pound has a large acid dissociation constant, consequently, its water solution is acidic and the solution of its sodium salt is less alkaline than that of any other commonly used sulfonamide. Because of sulfacetamide's high solubility and ready elimination, it has

found considerable use in urinary tract infections since it is possible to maintain high urinary concentrations without danger of kidney damage.

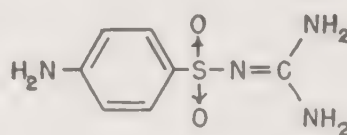
Sodium Sulfacetamide (Sodium *N*¹-acetyl-4-aminobenzenesulfonamide, Sodium sulamyd, Albucid soluble, Sodium *N*¹-acetylsulfanilamide).



Sodium Sulfacetamide

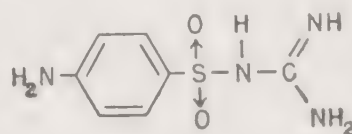
Sodium sulfacetamide is very soluble in water, and because of the favorable pH of solutions of this compound, it can be used at high concentration at the physiologic pH of 7.4. It is nonirritating to mucous membranes and has proved effective in the treatment of eye infections due to a number of different organisms.

Sulfaguanidine U.S.P. (Sulfanilylguanidine monohydrate, *N*¹-Guanylsulfanilamide) is a white, crystalline powder, nearly odorless, stable in air, but it slowly darkens on exposure to light.



Sulfaguanidine

This structure is preferred to the one frequently written for sulfaguanidine, for in

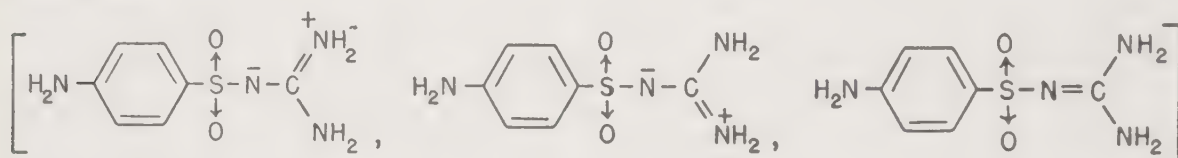


the latter there is both an acidic and a basic group in the same molecule. The hydrogen on the nitrogen next to the SO₂ group would be fairly acidic due mainly to the SO₂

group, but is attracted by the negativity of

the other two nitrogen atoms. The $\begin{array}{c} \text{NH} \\ \parallel \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$

group is essentially an amidine which is a fairly strong base ($K_b \sim 10^{-2}$) due to the two resonating forms of equal energy in the ion. Therefore, the two structures are incompatible in the same molecule, as one would neutralize the other, giving rise to the structures



which can resonate with each other. The last of these is the most stable due to the absence of a separation of charge and is the preferred structure if just one is to be written.

Sulfaguanidine is soluble in water, 1:1,000 at 25° C. and 1:10 at 100° C. It is sparingly soluble in alcohol and in acetone, is freely soluble in dilute acids, insoluble in nonpolar solvents such as benzene, ether and chloroform and insoluble in dilute bases. Hot, strongly basic solutions hydrolyze the compound to sulfanilamide and ammonia.

Sulfaguanidine was the first sulfonamide to be developed that was relatively soluble yet poorly absorbed into the blood stream. As a result, it can be used to counteract infections in the intestine, for example, bacillary dysentery, by oral administration without developing a high blood level concentration of the drug. Suggestions have been made to account for the lack of absorption despite high solubility, but a convincing explanation of the behavior of the compound has yet to be given.

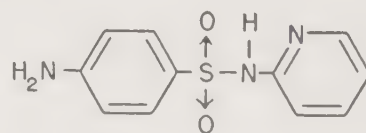
Sulfaguanidine has a comparatively low toxicity, however, various toxic manifestations such as vomiting, drug rash and fever, etc., are not uncommon. These reactions appear to be more frequent than are obtained

from the administration of sulfasuxidine and sulfathalidine.

The initial dose is 0.05 Gm. per kilogram of body weight followed by a like dose every four hours until the condition is abated. The total period of dosage should not exceed fourteen days. The average dose is 2 Gm.

Sulfapyridine, N.F., (2-Sulfanilamido-pyridine, N¹-2-Pyridylsulfanilamide, Dagenan, M. & B. 693, Coccoclast) is a white, odorless powder. It is stable in air but slowly darkens on exposure to light. It is soluble

in water (1:3,500), in alcohol (1:440) and in acetone (1:65). It is freely soluble in dilute acids and bases.



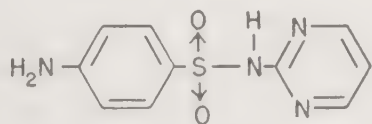
Sulfapyridine

Sulfapyridine was first proposed for use in 1937 by Whitby in England, and although it was used quite extensively at one time for the treatment of a number of infections, particularly pneumonia, it has largely been replaced in this country by sulfadiazine, sulfathiazol and sulfamerazine. The drug is acetylated quite readily in the body, and a number of cases of kidney damage have resulted from the acetylsulfapyridine crystals deposited in the kidneys. When the drug is given, the urinary output should be kept at 1,000 cc. or more per day to lessen the chances of calculus formation. The initial dose is 4 Gm. followed by 1 Gm. every four hours by mouth until the temperature is normal for seventy-two hours. Blood level concentrations of 4 to 6 mg. per 100 cc. should be maintained.

Sulfapyridine Sodium N.F. is a white, odorless crystalline powder, soluble in water (1:1.5) and in alcohol (1:10). Its water solutions have a pH of about 11 and absorb carbon dioxide from the air with precipitation of sulfapyridine. The compound is decomposed by light. Its uses are the same as those of sodium sulfadiazine.

The high pH of the sodium sulfa drugs, with the exception of sodium sulfacetamide, causes them to be damaging to tissues, results in incompatibilities with any acidic substance and brings about decomposition of most vasoconstrictors (two exceptions are desoxyephedrine and paredrine). They cannot be used in high concentrations on nasal or other membranes and must be injected intravenously with considerable care. Injections outside the vein may cause necrosis of the tissues. The free sulfa drugs can be used with most pressors, and the concentrations of sulfa drugs are high enough to be bacteriostatic. However, there is some doubt about the value of such use of sulfa drugs considering the possibilities of inducing sensitization.

Sulfadiazine U.S.P. (2-Sulfanilamidopyrimidine, N¹-2-Pyrimidylsulfanilamide).



Sulfadiazine

Sulfadiazine is a white, odorless, crystalline powder soluble in water (1:3,140 at 37° C.). It is soluble in dilute acids and bases and sparingly soluble in alcohol and acetone. Of the various sulfonamides, sulfadiazine is one of the most potent bacteriostatic agents and at the same time it exhibits fewer toxic reactions than most of the other sulfonamides. Its rate of absorption from the gastro-intestinal tract is slower and it is acetylated to a lesser degree in the blood and tissues than sulfanilamide, sulfathiazole or sulfapyridine. It is relatively easy to maintain high blood levels of sulfadiazine because of its

concentration in the blood as compared with most other body fluids. Sulfadiazine and acetylsulfadiazine are both excreted readily by the kidneys. Because of its various favorable properties, sulfadiazine is considered the sulfonamide of choice in a number of infections. These include hemolytic streptococcus infections due to Lancefields Group A organisms, pneumococcic, meningococcic, Friedlander's bacillus, *Shigella dispar* and *H. influenza* infections.

The initial dose is based on 0.1 Gm. per kilogram of body weight; this is followed by 1 Gm. every four hours until the temperature has been normal for five days. Preferably, the dosage should be controlled by determining the blood concentration of the drug. In severe infections, concentrations of about 15 mg. of sulfadiazine per hundred cubic centimeters of blood (15 mg. per cent) should be maintained. Because of its low solubility, the drug is administered by the oral route.

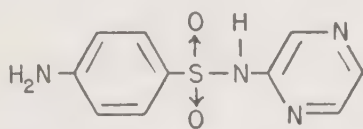
Since the solubility of sulfadiazine and its acetyl derivative increases rapidly as the pH is raised, it is advisable to alkalinize the urine by giving sodium bicarbonate, thus decreasing the possibility of precipitation in the kidney tubules, with resulting kidney damage.

Trisulfonamides. Recently, a mixture of three sulfonamides, such as sulfadiazine, sulfamerazine and sulfathiazole, has been used to reduce the possibilities of crystaluria. By employing the same total amount of the three different compounds, the same therapeutic level of total sulfonamide can be maintained, but since the concentration of each specific compound is only one-third, the possibility of precipitation of the acetyl-derivatives in the kidneys is greatly reduced.

Sulfadiazine Sodium U.S.P. is a white, odorless powder, soluble in water 1:2 and only slightly soluble in alcohol. Its water solutions are alkaline, with a pH of about 10, and they tend to absorb dioxide from the air with the precipitation of sulfadiazine.

Sulfadiazine sodium may be administered as a 5 per cent solution in sterile water intravenously for patients requiring an immediate high blood level of the sulfonamide. The high pH of the water-solutions of the drug will cause tissue damage if given subcutaneously or intramuscularly, hence the drug should not be given by these routes.

Sulfapyrazine N.N.R. (2-Sulfanilamidopyrazine, N¹-2-Pyrazinylsulfanilamide) is a tasteless, odorless, white crystalline powder which may become dark on exposure to light.

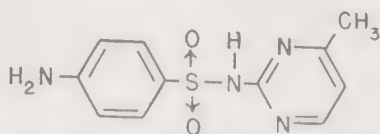


Sulfapyrazine

It is almost insoluble in water (1:20,000) and in ether and chloroform, is very slightly soluble in alcohol and slightly soluble in acetone. It is soluble in dilute acids and bases. Sulfapyrazine is absorbed and excreted rather slowly; thus, high blood levels are not obtained with single large oral doses. The drug is not acetylated readily in the body. It goes into the cerebrospinal and other body fluids, reaching concentrations from one-half to two-thirds of the blood level concentration within a half day.

Sulfapyrazine appears to be effective against *Shigella paradyserteriae* and it is about as effective as sulfadiazine in the treatment of hemolytic streptococcal, *B. coli* and pneumococcal infections. The initial dose is 2 Gm. followed by 1 Gm. every four to six hours. One to 4 Gm. of sodium bicarbonate usually are given with each dose.

Sulfamerazine U.S.P. [2-Sulfanilamido-4-methylpyrimidine, N¹-(4-methyl-2-pyrimidyl)sulfanilamide]. Sulfamerazine is a white, crystalline compound with a slightly bitter taste.



Sulfamerazine

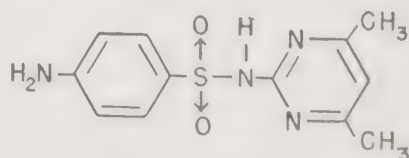
It slowly darkens on exposure to light. It dissolves in water, 1:6,250 at 20° C. and 1:3,300 at 37° C. It is readily soluble in dilute acids and bases, is sparingly soluble in acetone, slightly soluble in alcohol and very slightly soluble in chloroform and ether.

Sulfamerazine is absorbed more rapidly but excreted more slowly than sulfadiazine. It is also absorbed more completely, and the same blood concentrations of sulfonamide can be maintained by administering this drug less frequently and in smaller doses. Also, since both the drug itself as well as its acetyl derivative are more soluble in urine than sulfadiazine and its corresponding acetyl derivative, the possibility of renal injury is less with sulfamerazine if equal blood concentrations of the drugs are maintained. The average dose is 2 Gm. given with sodium bicarbonate.

Because of the above advantages, sulfamerazine may replace sulfadiazine as the sulfonamide of choice in the treatment of a number of infections. At the present time it is used in the treatment of streptococcal, pneumococcal, meningococcal and gonococcal infections.

Sulfamerazine Sodium U.S.P. is a white crystalline powder that slowly darkens on exposure to light. It is soluble in water (1:3), slightly soluble in alcohol and insoluble in ether. Its water solution has a pH of about 10, and upon long exposure to humid air, it absorbs carbon dioxide with the precipitation of sulfamerazine. The compound is used for the same purpose as sulfadiazine sodium.

Sulfamethazine [4,6-Dimethyl-2-sulfanilamidopyrimidine, N¹-(4,6-Dimethyl-2-pyrimidyl)sulfanilamide] is similar in action to

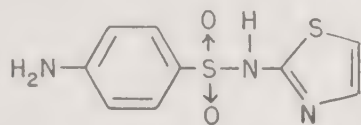


Sulfamethazine

sulfamerazine. It has a greater solubility in acid urine than the latter compound, thus

decreasing the possibility of kidney damage from use of the drug.

Sulfathiazole U.S.P. (2-Sulfanilamidothiazole, N¹-2-Thiazolylsulfanilamide, M. & B. 760, Thiazamide) is a white, crystalline, odorless compound. It is soluble in water (1:1,700) and (1:200) in alcohol at 25° C.



Sulfathiazole

It is soluble in acetone and freely soluble in dilute acids and bases.

Sulfathiazole is fairly evenly distributed throughout the body tissues. Its degree of acetylation in the tissues is usually greater than that noted for sulfanilamide. It is excreted rapidly by the kidneys, and sometimes adequate blood levels are difficult to maintain because of this.

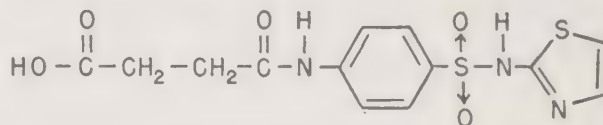
Sulfathiazole is the sulfonamide drug of choice in the treatment of gonococcal and staphylococcal infections. It shows toxic manifestations similar to those of sulfanilamide. The incidence of nausea, dizziness, vomiting, cyanosis and psychoses is low, but the drug produces more cases of rash and drug fever than any other commonly used sulfonamide. Hematuria and other kidney damage have been observed, due in some instances to the formation of acetylsulfathiazole crystals in the kidneys. To help prevent damage to the kidneys, the daily urinary output should be maintained at not less than 1,000 cc. in the course of therapy with this drug. To minimize the danger of kidney damage it is common practice to administer 1 to 4 Gm. of sodium bicarbonate each time the drug is administered.

The initial dose is usually 4 Gm.; this is followed by 1 Gm. every four hours until the temperature has been normal for seventy-two hours. As with the other sulfonamides, it is best to measure the blood level concentration of sulfathiazole by repeated determinations. Concentrations of

from 4 to 6 mg. per cent are considered satisfactory for most purposes.

Sulfathiazole Sodium U.S.P. is a white powder, soluble in water (1:2.5) and in alcohol (1:15). Its water solutions have a pH of about 10 and absorb carbon dioxide from the air, with the precipitation of sulfathiazole. The anhydrous salt can be sterilized but the mono- and sesquihydrates cannot. The uses are the same as those of sodium sulfadiazine.

Succinylsulfathiazole U.S.P. [2-(N⁴-Succinylsulfanilamido)-thiazole, Sulfasuxidine] is a white, crystalline powder, odorless and stable in air, but it slowly darkens on exposure to light. It dissolves in water (1:4,800), is sparingly soluble in alcohol and acetone and insoluble in chloroform and ether. It is soluble in dilute bases and dissolves in solutions of sodium bicarbonate with the evolution of carbon dioxide.

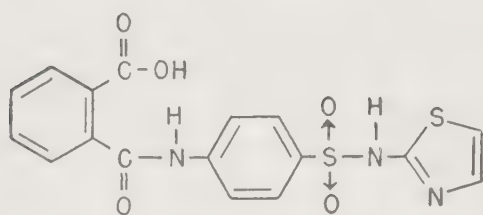


Succinylsulfathiazole

Succinylsulfathiazole is poorly absorbed from the intestinal tract. Since its toxicity is less than that of sulfaguanidine, it has value as an intestinal bacteriostatic agent. It is used in pre-operative preparation and post-operative treatment of patients requiring surgery on the intestinal tract, as well as in the treatment of bacillary dysentery.

Initial dosage is 0.25 Gm. per kilo of body weight by mouth followed by 0.25 Gm. per kilo daily given in six equal portions at four hour intervals.

Phthalylsulfathiazole N.N.R. [Sulfathalidine, 2-(N⁴-Phthalyl-sulfanilamido)thiazole] is an odorless, white, crystalline powder with a slightly bitter taste. It slowly darkens on exposure to light. It is insoluble in water and chloroform and slightly soluble in alcohol. It is readily soluble in bases and in concentrated hydrochloric acid.



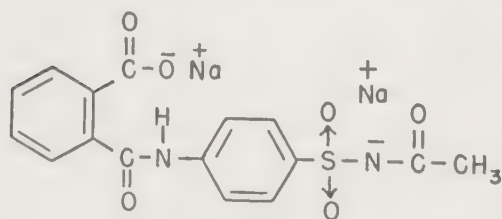
Phthalylsulfathiazole

This compound, like succinylsulfathiazole, is poorly absorbed from the intestinal tract. Only about five per cent of the phthalylsulfathiazole is absorbed, with the result that blood levels of more than 1.5 mg. per 100 cc. are rarely encountered with the usual doses. This amount is excreted by the kidneys, chiefly in conjugated forms which are soluble in acid urine, thus being relatively free from the possibilities of developing crystalluria.

It is used as an adjunct in the treatment of inflammatory diseases of the intestinal tract, including acute and chronic ulcerative colitis and regional ileitis. It is employed as a preliminary adjunct to intestinal surgery, but is not recommended for elimination of the carrier state or for acute bacillary dysentery.

The dose is 0.05 to 0.1 Gm. per kilogram of body weight daily, taken orally.

Sodium Phthalylsulfacetamide (Disodium N^1 -Acetyl- N^4 -phthalylsulfanilamide)

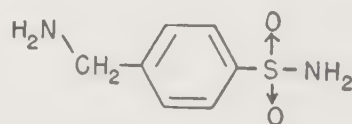


Sodium Phthalylsulfacetamide

is said to have the unique property of being highly absorbed into the intestinal wall without getting into the blood stream in appreciable concentrations. Thus, the compound is used in the treatment of enteric infections where it can provide a high concentration of a bactericidal compound at the locus of infection without involving a high

blood level or a high concentration in the intestinal contents.

Sulfamylon (*p*-Aminomethylbenzenesulfonamide, Homosulfanilamide, Marfanil, Mesudin) is not a true sulfanilamide-type compound in that the activity of the compound is not inhibited by *p*-aminobenzoic acid. This behavior is in keeping with the fact that the amino group is not attached directly to the ring. The action of sulfamylon as a bacteriostatic agent involves a different mechanism from that of a sulfanilamide-type compound. It is particularly effective against *Cl. welchi* in topical application. It was used as a topical bacteriostatic agent by the Germans during World War II, alone and in combination with sulfanilamide.



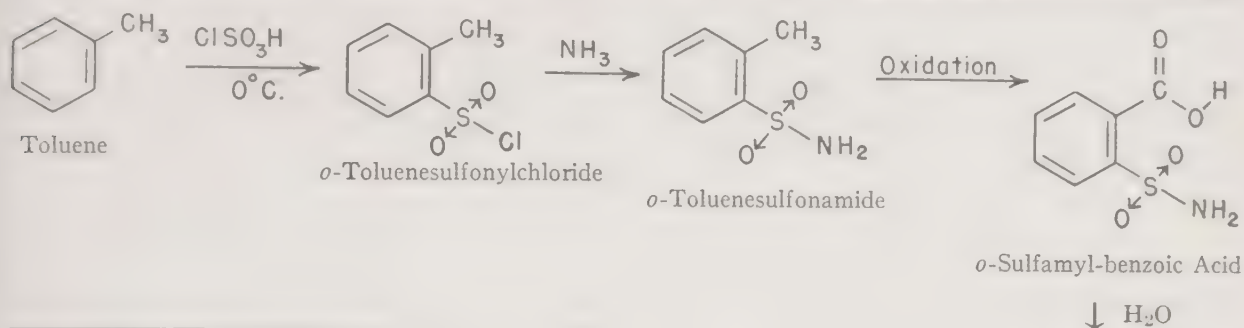
Sulfamylon

Saccharin (Gluside, Benzosulfimide) U.S.P. (*o*-Benzosulfimide). Saccharin occurs as a white crystal, or a white crystalline powder. It is odorless or nearly so, but has a very pronounced sweet taste.

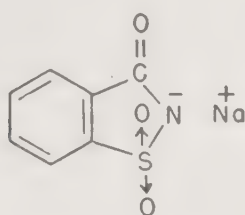
For the preparation of saccharin, see the equations at the top of page 257.

In dilute solution it is about five hundred times as sweet as sucrose. The compound is acidic ($K_a = 2.5 \times 10^{-2}$) due to the presence of the negative CO and SO₂ groups next to the NH group. It is soluble in water (1:290), in alcohol (1:31) and in dilute base. Since it does not enter into the body metabolism, it is employed as a sweetening agent in the diets of diabetics and others who should not eat much sugar.

Saccharin Sodium U.S.P. (Sodium benzosulfimide, Soluble Saccharin) occurs as a white crystalline powder. It is soluble in water (1:1.5) and in alcohol (1:50). Like saccharin, the sodium salt is about five hundred times as sweet as sugar and since the



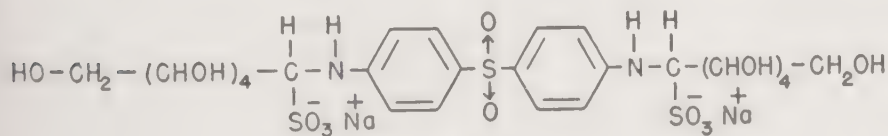
salt is much more soluble in water, this is the form in which it is usually employed as a sweetening agent.



Saccharin Sodium

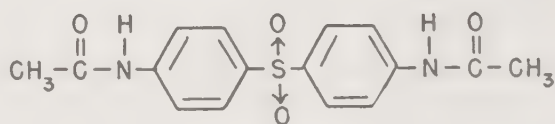
SULFONES

Promin [*p,p'*-Diaminodiphenylsulfone- N,N^1 -Di(dextrose sodium sulfonate)] occurs as a white powder. It is soluble in water, the solutions being sufficiently stable so they can be sterilized by heat. Promin is active against tuberculosis and leprosy and is used in the treatment of these conditions. It is injected intravenously and applied topically. The average dose is from 2 to 5 Gm. daily.



Promin

Rodilone (4,4'-Diacetamidodiphenylsulfone) is claimed to be less toxic and less active than the parent diaminodiphenylsulfone, which is about one hundred times as active a bacteriostatic agent as sulfanilamide. It is used in France for the treatment of gonorrhea.

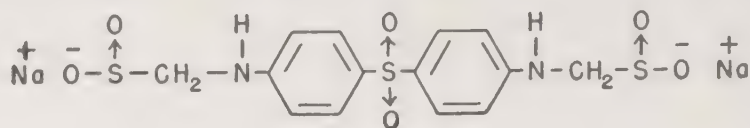


Rodilone

Diasone (4,4'-Diaminodiphenylsulfone-di-N-methanal sulfoxylate) has been used in the treatment of tuberculosis and is said to show effects comparable to those of Promin.

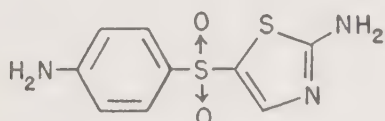
The formula for diasone is shown at the top of page 258.

Promizole (4,2'-Diaminophenyl-5'-thiazole sulfone), although not a direct derivative of 4,4'-diaminodiphenylsulfone as are the above three compounds, is, however, an isostere of this compound. Promizole acts at a lower dosage level than the



Diasone

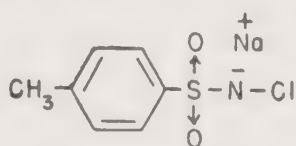
above compounds and its toxicity is less.



Promizole

Although these sulfones represent a good start in the development of chemotherapeutic agents for the treatment of tuberculosis, it is probable that in the not too distant future much more effective compounds will be found for this purpose.

Chloramine-T, N.F. (Sodium *p*-toluenesulfonchloramide, Chloramine) is a crystalline powder, soluble in water (1:7) and in alcohol, but insoluble in ether and chloroform. It has a slight odor of chlorine and its solutions decompose, liberating chlorine. This decomposition is very rapid in the presence of acids or acidic substances.

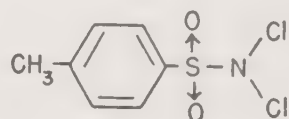


Chloramine-T

It is used like the inorganic hypochlorites as an antiseptic and disinfectant but is less irritant. It is applied to mucous membranes as a 0.1 per cent aqueous solution and is used to irrigate or dress wounds as a 1 per cent solution.

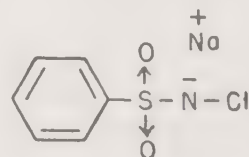
Dichloramine-T, N.F. (*p*-Toluenesulfondichloramide) occurs as white or greenish-yellow crystals or as a crystalline powder having the odor of chlorine. It is almost insoluble in water but is soluble in alcohol. It is soluble in petroleum benzin (1:1), in

chloroform (1:1), in carbon tetrachloride (1:2.5) and in eucalyptol or chlorinated paraffin. Dichloramine-T is used for the same purpose as Chloramine-T. A one per cent solution in chlorinated paraffin is used for application to mucous surfaces, and a five per cent solution in the same solvent is used in dressing wounds.



Dichloramine-T

Chloramine-B (Sodium Salt of Benzene-sulfonamide Chloride) is another compound whose disinfectant powers depend on the presence of "active chlorine" or the release of "nascent" chlorine by hydrolysis.

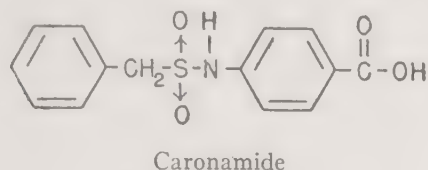


Chloramine-B

Halazone N.F. (*p*-Sulfondichloramido-benzoic Acid, *p*-Carboxysulfondichloramide) is a white crystalline powder with a chlorine-like odor. It is affected by light. It is slightly soluble in water and chloroform and is soluble in dilute alkalis. The sodium salt of the compound is used in sterilizing drinking water.

Caronamide (4'-Carboxyphenylmethanesulfonanilide) is a colorless, crystalline compound with little or no taste or odor. It is slightly soluble in water, carbon tetrachloride, chloroform or benzene, and is fairly

soluble in alcohol and propylene glycol. Both the mono- and di-sodium salt are very soluble in water. The compound is relatively stable to hydrolysis with either acids or bases.



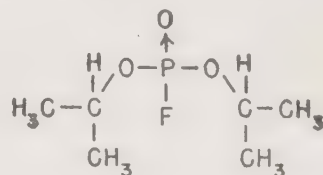
Caronamide is being used to decrease the rate of excretion of penicillin¹⁶ and thus aid in maintaining more effective blood concentrations over a longer period of time from the same dose of penicillin. Eighty per cent of penicillin in the body is lost by tubular excretion and twenty per cent by way of the glomerulus. Caronamide combines with the enzyme responsible for tubular excretion of penicillin, thereby preventing the antibiotic from being excreted by this route. Caronamide itself is eliminated exclusively by glomerular filtration. The LD₅₀ by the intravenous route is 1405 mg./kg. for mice; thus, it has a toxicity intermediate between that of sodium penicillin G with an LD₅₀ of 3090 mg./kg. and potassium penicillin G with an LD₅₀ of 564 mg./kg.

PHOSPHORUS COMPOUNDS

Organic phosphorus compounds have been of little importance as pharmaceutical or therapeutic agents. For many years it has been known that phosphorus was present in such compounds as the phosphoproteins and phospholipids. It was only in the last two decades, however, that the very important role phosphoric acid derivatives play in a number of enzyme systems became known. Compounds such as adenosinetriphosphate, phosphopyruvate and acetylphosphate have been shown to be key compounds in energy transfers involved in the metabolism of foodstuffs. Phosphorus compounds play a role in muscle contraction, fatty acid oxidation, carbon dioxide fixation and drug detoxications.¹⁷

The extreme importance of phosphorus compounds for these vital physiologic processes, coupled with the fact that a number of types of drugs have been shown to owe their therapeutic effect to their being sufficiently like some essential metabolite so they can displace it (competitive inhibition) but sufficiently different so that characteristic action of the essential metabolite is not duplicated¹⁸ (metabolic antagonists), suggests that among phosphorus compounds there may be discovered in the near future some valuable therapeutic agents. A few phosphorus compounds have recently been studied. One of these has value as a therapeutic agent, and others are being used as insecticides.

Diisopropyl Fluorophosphate, DFP, is a colorless liquid, soluble in water to the extent of 1.54 per cent at 25° C. It is soluble in alcohol and to some extent in peanut oil.



It is stable in the latter for a period of one year, but decomposes in water in a few days. Solutions in peanut oil can be sterilized in an autoclave. The compound should be stored in hard glass since continued contact with soft glass is said to hasten decomposition, as evidenced by a discoloration.

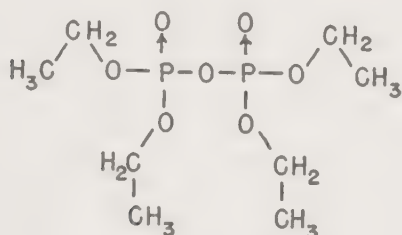
The compound was studied for possible use as a war gas and was found to be a very potent lethal inhalant. It has strong anticholinesterase activity,¹⁹ and appears to act by destroying cholinesterase rather than temporarily inactivating it by the formation of a reversible combination. Its effect is similar to that of neostigmine and eserine (parasympathomimetic agents), but the duration of action is more prolonged, lasting for days or even weeks. Its longer action is thought to depend on the fact that it destroys the cholinesterase, and action is only

restored when new cholinesterase is synthesized in plasma and the erythrocytes and other cells.

DFP has been used clinically in the treatment of myasthenia gravis and glaucoma.

A combination of atropine sulfate and magnesium sulfate has been found to give the best protection in rabbits against the toxic effects of DFP. One counteracts the muscarine and the other the nicotinic effect of the drug.²⁰

Hexaethyltetraphosphate, HETP, and Tetraethylpyrophosphate are compounds that also show anticholinesterase activity. HETP was developed by the Germans during World War II and was used as an insecticide against aphids. Recently, it has been reported that some HETP being sold in this country does not have this structure but is a mixture of which the active constituent is tetraethylpyrophosphate.



Tetraethylpyrophosphate

When used as insecticides, these compounds have the advantage of being hydrolyzed rapidly to the relatively nontoxic water-soluble compounds, phosphoric acid and ethyl alcohol. Fruit trees or vegetables sprayed with this type of compound retain no harmful residue after a period of a few days or weeks, depending on the weather conditions. The disadvantage of their use comes from their very high toxicity, which results mainly from their anticholinesterase activity. Workers spraying with these agents should use extreme caution that none of the vapors are breathed and that none of the vapor or liquid comes in contact with the eyes or skin.

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18

Compounds Containing Metals

SILVER COMPOUNDS

MERCURY COMPOUNDS

ARSENIC COMPOUNDS

AROMATIC ARSENICALS

PENTAVALENT AROMATIC ARSENICALS

TRIVALENT ARSENIC COMPOUNDS

ANTIMONY COMPOUNDS

BISMUTH COMPOUNDS

INSOLUBLE COMPOUNDS

WATER-SOLUBLE COMPOUNDS

OIL-SOLUBLE COMPOUNDS

GOLD COMPOUNDS

TIN COMPOUNDS

SILVER COMPOUNDS

Silver was one of the first metals discovered by man, and although the metal and its compounds have been used since early times for the treatment of various conditions and diseases, their use at present is confined to local applications as antiseptics and germicides.

The silver compounds may be divided into several classes: those in which the silver is mainly in the ionic form, as in silver nitrate, lactate and picrate; those in which the silver is largely nonionized and in colloidal suspension, as in Mild Silver Protein, U.S.P.; those in which an insoluble compound of silver is in a colloidal form, as in colloidal silver chloride.

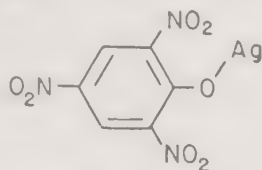
The ionized compounds, like silver lactate,

are the most bactericidal, but are also the most caustic, and since they are precipitated by proteins and chlorides, their use is largely confined to the surface of the body.

The colloidal silver proteinate preparations are divided into two types, the strong silver proteins and the mild silver proteins. The former type contains about 8 per cent silver, but the silver is apparently more ionized than in the mild silver protein preparations, which contain about 20 per cent silver.

Silver has an oligodynamic effect resulting in a prolonged activity with very low concentrations. The long-continued use of all silver preparations involves the possibility that the patient may develop argyria—a gray discoloration of the skin, conjunctiva and internal organs.

Silver Picrate (Picragol) N.N.R. (Silver Trinitrophenolate) is used in the treatment of urethritis, etc., usually in one to two per cent dilutions in a dusting powder or in suppositories.



Silver Picrate

Silver Lactate is somewhat less caustic than silver nitrate and is used as an antiseptic in dilutions of 1:100 to 1:4,000. It is light-sensitive and should be kept in dark bottles.

Strong Protein Silver (Strong Silver Protein, Strong Protargin) N. F., (Silver Proteinate, Protargol, Silver Protein Strong). Strong Protein Silver occurs as an orange or brown, odorless powder. It is affected by light and is freely soluble in water but almost insoluble in alcohol, ether and chloroform. It contains about eight per cent silver and is made by treating a silver nitrate solution with an excess of a purified protein solution, filtering the precipitate, redissolving (peptizing) it in water and evaporating to dryness under a vacuum. It is used in treating infectious conditions of the mucous membranes, for example, rhinitis, proctitis, conjunctivitis and tonsillitis. Concentrations of 0.5 to 10 per cent in distilled water are used.

Solutions should be freshly prepared and dispensed in amber bottles.

Mild Silver Protein (Mild Protein Silver, Mild Protargin) U.S.P. (Argyn, Argyrol, Cargentos, Lunargen, Sarcol, Silvol, Solar-gentum) occurs as dark-brown or black scales or granules. It is odorless, affected by light and is freely soluble in water but almost insoluble in organic solvents. It contains about twenty per cent silver held in colloidal suspension by a protein acting as a protective colloid. It is used in treating the same conditions as the strong silver proteins but is much less irritating than the latter. The concen-

trations used vary from three to fifty per cent. Since the discovery of penicillin and the sulfonamide drugs, the use of silver protein compounds has decreased.

Colloidal Silver Iodide N.F. (Neo-Silvol) is a pale yellow substance containing about twenty per cent silver iodide with gelatin. It is freely soluble in water in which the gelatin holds the silver iodide as a colloidal suspension. Solutions of colloidal silver iodide are sensitive to light and should be kept in amber-colored bottles. It is used in treating infections of the mucous membranes and is supposed to have mild antiseptic properties. It is nonirritating and is used in concentrations as high as fifty per cent.

Colloidal Silver Chloride N.F. (Lunisol) is a white, granular powder containing about ten per cent silver chloride, which is rendered colloidal by the presence of some stabilizing agent such as sucrose. It is odorless, has a sweet taste and is affected by light. It is used for the same purposes as colloidal silver iodide.

Silver Hexamethylenetetramine (Argentiform) is a white, crystalline powder soluble in water (1:500). It is used as a 0.2 to one per cent ointment in the treatment of conjunctivitis and urethritis. It is presumed to combine the antiseptic action of silver with that of hexamethylenetetramine.

Silver Hexamethylenetetramine Nitrate (Argolavol) is very soluble in water. It is used topically in one to fifty per cent solution or as an ointment in the treatment of various infections including those of the eye and the genito-urinary tract.

MERCURY COMPOUNDS

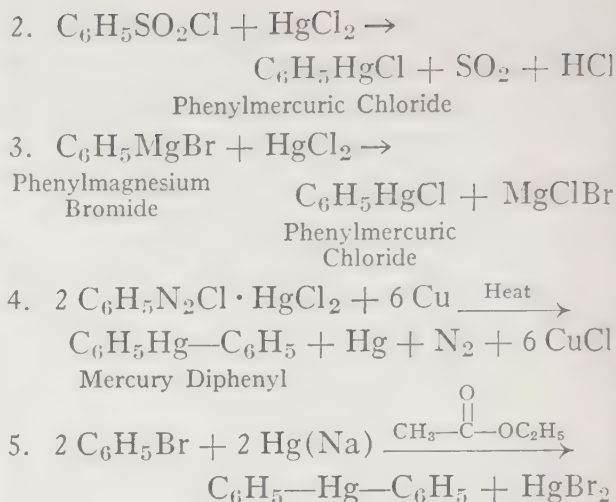
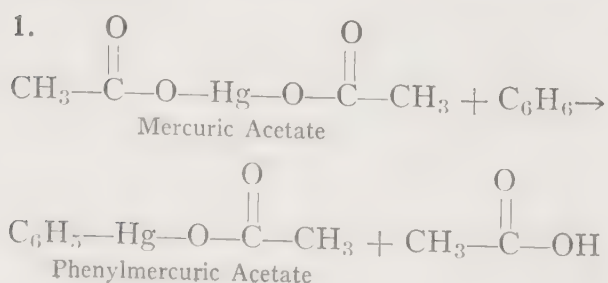
Mercury and its compounds have been used since early times in the treatment of various diseases. Metallic mercury incorporated in ointment bases was applied locally for the treatment of skin infections and syphilis. A few inorganic mercury compounds have been used orally but are no longer commonly used because of the gastro-

intestinal disturbances and other toxic manifestations resulting therefrom. A number of organic mercury compounds are now in use mainly as antiseptics, disinfectants and diuretics. In some of these the mercury is attached to carbon and is rather firmly held to the organic portion of the molecule, in others the mercury is attached to oxygen or nitrogen and may be almost completely or partially ionized.

At present it appears¹ that the antibacterial action of mercury compounds is best explained on the basis of their interfering with SH (sulfhydryl) compounds that are essential cellular metabolites. Large concentrations of SH compounds will completely inactivate mercury compounds as far as their bactericidal or bacteriostatic action is concerned. This reaction is reversible. Apparently mercury compounds inhibit the growth of bacteria because the mercury combines with SH groups to form a complex of the type $R-S-Hg-R$, thus depriving the cell of the SH groups necessary for its metabolism. However, if other SH-containing compounds are introduced which take the mercury away from the bacteria, the latter can grow again.

Experiments have been carried out in which bacteria that have been rendered inactive by mercury compounds have resumed growth when treated with hydrogen sulfide, thioglycollic acid and other sulfhydryl compounds. Thus, apparently the mercury compounds are not bactericidal but only bacteriostatic in character. It would appear then that they are not very effective antiseptics or germicidal agents.

Organic compounds of mercury can be made in a number of ways, including the following:



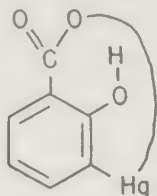
The C—Hg linkages are broken by strong acids, halogens and thiocyanogen $(\text{SCN})_2$. The active metals replace mercury; thus, phenyl compounds of sodium, magnesium, zinc, etc., may be made from the mercury compounds. The halides of nonmetals such as phosphorus, arsenic and boron react with mercury diphenyl to give phenyl derivatives of the nonmetal, one or more of the halogen atoms being replaced by phenyl, depending on the conditions. Diphenyl mercury is stable to compounds containing active hydrogen, for example, water, hydrogen sulfide, alcohols and ammonia, which decompose C—Mg linkages.

Mercuric Cyanide N.F. $[\text{Hg}(\text{CN})_2]$, **Mercuric Oxycyanide** $[\text{Hg}(\text{CN})_2 \cdot \text{HgO}]$. These compounds are used in place of mercuric chloride as disinfectants. Their use is somewhat limited, however, because of their toxicity, corrosive action on metals and tendency to precipitate proteins. The oxycyanide is said to have less effect on metals and proteins than the other compound.

Mercuric Benzoate $[(\text{C}_6\text{H}_5\text{COO})_2\text{Hg} \cdot \text{H}_2\text{O}]$ has been used locally in the treatment of gonorrhea in 1:2,000 or 1:1,000 dilutions and intramuscularly in one or two per cent solutions for the treatment of syphilis. It has been largely replaced by other agents or by mercury compounds in which the mercury is attached to carbon.

Mercuric Salicylate N.F. occurs as a white, yellowish or pink, odorless powder. It is affected by light, is insoluble in water

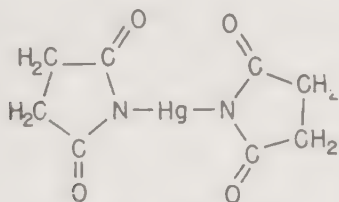
and alcohol, but dissolves in bases. The structure above is the one usually given for the compound, but it undoubtedly is incorrect because it requires a Hg—O bond distance of about 5 Å which is far too long. It



Mercuric Salicylate

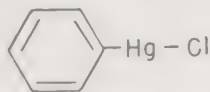
is used by intramuscular injection in the treatment of syphilis, but is rather painful and various local anesthetics are sometimes added to reduce the pain.

Mercuric Succinimide N.F. occurs as white crystals or as a white powder. It is readily decomposed by acids, halogens and hydrogen sulfide. It is odorless but darkens on exposure to light. It is soluble in water (1:20), is slightly soluble in alcohol and is insoluble in ether. It is used by intramuscular injection in the treatment of syphilis.



Mercuric Succinimide

Phenylmercuric Chloride N.F. occurs as white, leafy crystals that are affected by light. It is practically insoluble in water but is slightly soluble in hot alcohol.



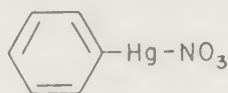
Phenylmercuric Chloride

In general, compounds of this type are ionized in solution to give phenylmercuric ions ($C_6H_5Hg^+$) and the compounds are thought to owe their bacteriostatic properties to these ions. Because of its low solubility, phenylmercuric chloride has been largely

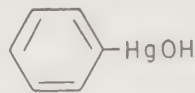
replaced by more soluble compounds such as phenylmercuric nitrate or borate. Phenylmercuric salts are used in buffered aqueous solutions because in this form they are more stable and less irritating. Since the compounds are more stable in acid than in alkaline solutions, slightly acidic solutions are sometimes employed. In general, the solutions are noncorrosive to rubber and most metals, except aluminum, and are odorless, stainless and colorless. The compounds have a fairly high bacteriostatic index against a number of pathogenic organisms but have a relatively low toxicity to human tissue. They do not, however, kill bacterial spores even after exposure for several hours.

Upon long standing, solutions of phenylmercuric salts may show the presence of mercuric and mercurous ions. The presence of metallic mercury is evidence of extensive decomposition.

Phenylmercuric Nitrate N.F. (Merphenyl Nitrate) occurs as a white, crystalline powder and is a mixture of phenylmer-



Phenylmercuric Nitrate

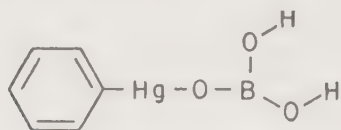


Phenylmercuric Hydroxide

curic nitrate and phenylmercuric hydroxide. It is very slightly soluble in water and slightly soluble in alcohol and glycerine. It is used in 1:1,500 to 1:24,000 aqueous buffered solutions. The former concentration is for disinfection of intact skin or minor abrasions, the more dilute concentration is for application to mucous membranes or wet dressings or continuous irrigation of wounds. It also is used in a concentration of 1:1,500 in an oxycholesterin base ointment for the treatment of superficial infections and minor lesions.

Phenylmercuric Borate N.N.R. (Merphenyl Borate) is used in concentrations of 1:500 as a tincture consisting of 4.6 per cent acetone 43.2 per cent alcohol, 50 per cent water and containing 1 per cent boric acid and 1 per cent sodium acid phosphate. The

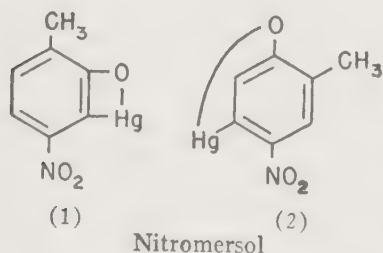
full strength tincture is used for disinfection of the skin and in the treatment of superficial wounds and injuries. For application to mucous membranes, use on wet dressings



Phenylmercuric Borate

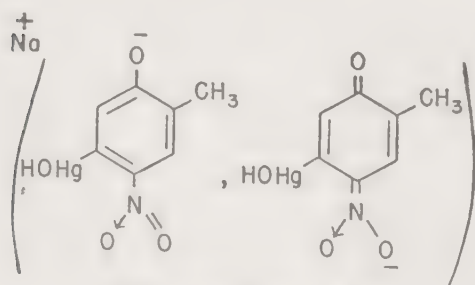
and wound irrigation, a 1:24,000 concentration is used. Solutions of this compound are supposed to be less irritating than some other phenylmercuric compounds.

Nitromersol N.F. (Metaphen, 4-Nitro-5-hydroxymercuri-2-methyl phenol anhydride) occurs as a yellow powder that is practically insoluble in water and has a low solubility in alcohol, acetone and ether. It dissolves in alkalis due to the formation of a salt. Two of the structures for the compound given in the literature are (1) and (2). The N.F. and the N.N.R. give formula (1). It is very probable that neither of these



Nitromersol

structures is correct. In (2) there is too great a distance between the Hg and O for the formation of a bond, and in (1) the normal valence angle of 180° for mercury would have to be greatly distorted to form the four-membered ring. The forms in which



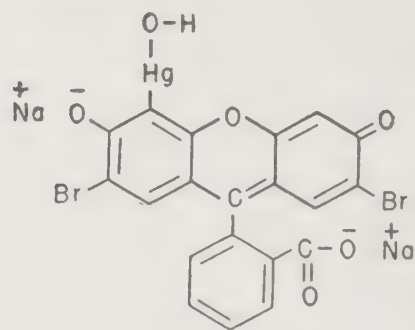
Nitromersol Sodium Salt

it is most commonly supplied are a 1:500 aqueous solution and a 1:200 alcohol-acetone-aqueous solution, in both of which the compound is present as the sodium salt.

Nitromersol is used mainly for the disinfection of the skin and for application to mucous membranes. It is also available in various other forms, for example, a 1:5,000 to 1:1,000 solution in oil, a 1:3,000 ophthalmic ointment, a 1:5,000 solution with one per cent ephedrine, etc.

Chloromercuri Carvacrol (Chloromer-crol) is supplied as a one per cent ointment that is used as a fungicide in the treatment of such conditions as athletes foot.

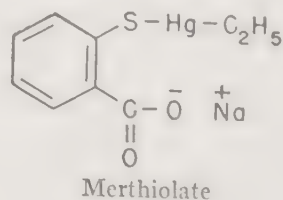
Merbromin N.F. (Mercurochrome, Disodium-2,7-dibromo-4-hydroxymercurifluorescein) was one of the first organic mercurials used as a general antiseptic. It is freely soluble in water, nearly insoluble in alcohol and acetone and insoluble in ether and chloroform. It is a nonirritating antiseptic that is used for the disinfection of wounds, the



Merbromin

skin and mucous surfaces. It is used as a two per cent aqueous solution and as a two per cent aqueous-acetone-alcohol solution, called surgical merbromin solution.

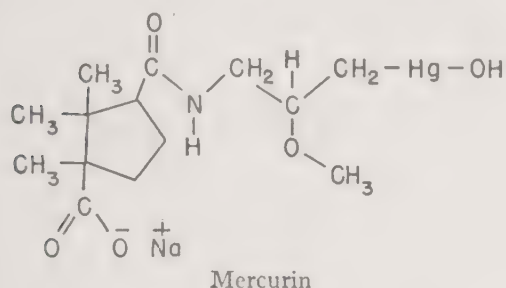
Merthiolate N.N.R. (Merthiolate sodium, Sodium Ethylmercurithiosalicylate) occurs as a cream-colored powder. It is soluble in water and is compatible with alcohol, soaps and physiologic salt solution. It does not



Merthiolate

stain fabric or tissues. It is used as an anti-septic in various ways: 1:1,000 tincture for skin disinfection, 1:1,000 aqueous solution for wounds and denuded surfaces, 1:5,000 in ophthalmic ointment, 1:20,000 to 1:5,000 aqueous for urethral irrigation, 1:5,000 to 1:2,000 aqueous for nasal mucous membranes

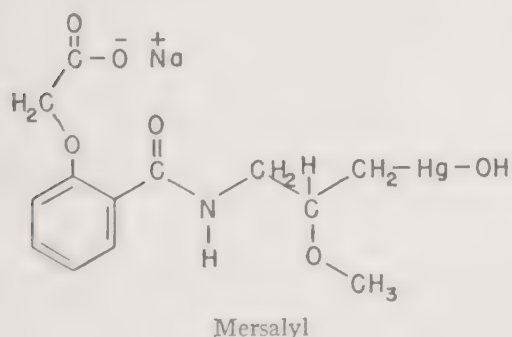
Mercurin (Sodium salt of β -methoxy- γ -hydroxymercuri propylamide of 2,2,3-trimethylcyclopentane-1,3-dicarboxylic acid) is



a diuretic which is administered in the form of suppositories.

Mercurphylline Injection U.S.P. (Mercuzanthin, Mercupurin) is a sterile solution in water of equal molecular proportions of mercurin and theophylline. The average dose by intramuscular injection is 0.1 Gm. of the mercuric compound and 40 mg. of theophylline. It is an effective diuretic.

Mersalyl U.S.P., Salyrgan, Sodium [o-(γ -hydroxymercuri- β -methoxypropyl-carbamyl) phenoxy] acetate, is an odorless, white, crystalline powder with a bitter taste.

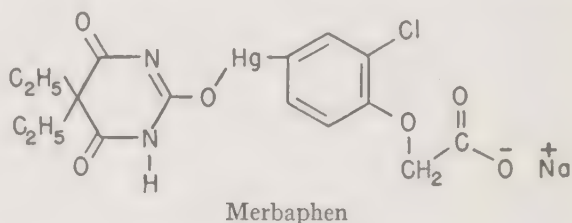


It is soluble 1:1 in water, 1:2 in alcohol and is insoluble in chloroform and ether. It is used as a diuretic.

Mersalyl and Theophylline Injection

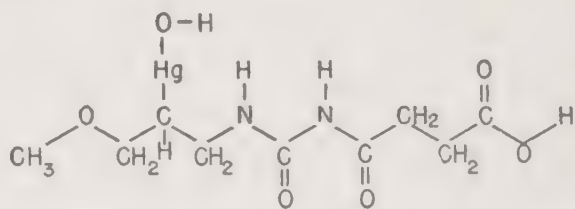
U.S.P. is a sterile solution of approximately two parts of mersalyl to one part of theophylline in water. It is employed as a diuretic. The average dose for intramuscular injection is 0.2 Gm. of mersalyl to 0.1 Gm. of theophylline.

Merbaphen (Novasurol) is a white crystalline powder that is soluble in water. It is



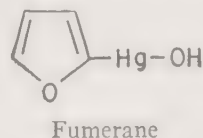
used as a diuretic in a ten per cent solution which is administered by intramuscular or intravenous injection.

Meralluride N.N.R. (Mercuryhydrin) is composed of approximately equal molecular quantities of 1-(γ -methoxy- β -oxymercuri-propyl)-3-succinyl urea and theophylline. It is used as a diuretic and is administered by intramuscular injection.



1-(γ -Methoxy- β -oxymercuri-propyl)-3-succinyl Urea

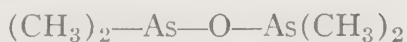
Fumerane (2-Hydroxymercurifuran) is used as an antiseptic. It has a low toxicity index and is reported to be bacteriostatic in dilutions of 1:9,000,000 against *Escherichia coli*.



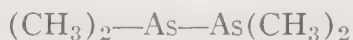
ARSENIC COMPOUNDS

A pharmacist, Louis Cadet, discovered the first organic arsenic compound in 1760. He heated arsenous acid and potassium acetate and obtained a fuming liquid with an offensive odor; this compound later was

shown by others to contain cacodyl oxide and cacodyl.



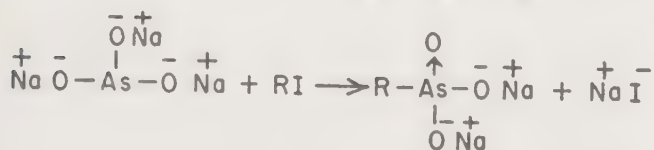
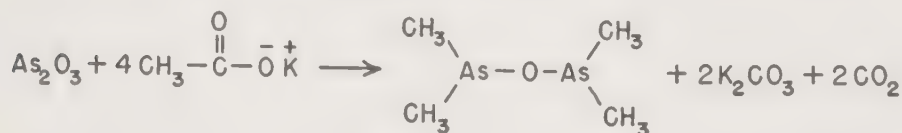
Cacodyl Oxide

Cacodyl, Dicacodyl
Tetramethyldiarsine

These compounds contain the cacodyl radical, $(\text{CH}_3)_2\text{As—}$, which was so named by Berzelius from the Greek word for stinking. They can be considered as derivatives of arsine, AsH_3 . Arsine and almost all of its derivatives are highly toxic.

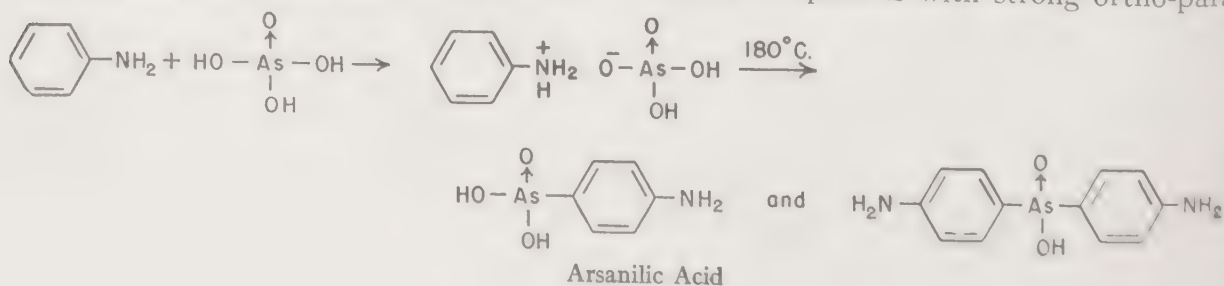
The halogen derivatives of arsine, methyl dichloroarsine, dimethylchloroarsine, etc., are more toxic than the unhalogenated compounds. The arsines, like the phosphines, show virtually no basic properties, in contrast to ammonia and its derivatives.

Aliphatic arsenic compounds may be made in the following ways:



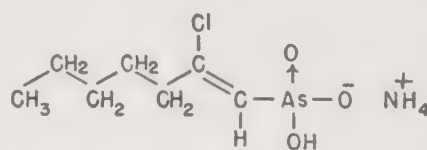
Sodium Cacodylate, N.F., $(\text{CH}_3)_2\text{—}\overset{\text{O}}{\parallel}\text{As—O—Na}^+$, is a white, crystalline, deliquescent compound. It has been used as a tonic in debilitating diseases and also in the treatment of syphilis.

Ferric Cacodylate N.F., $[(\text{CH}_3)_2\text{AsO}_2]_3\text{Fe}$, occurs as a yellowish amorphous powder.



It is soluble in water (1:30) and slightly soluble in alcohol. The product is of variable composition and may contain, in addition to molecules of the normal salt, those molecules in which one or more OH groups are also attached to Fe. It is used parenterally in the treatment of leukemias and secondary anemias. The average dose is 60 mg.

Chloroarsenol (Ammonium heptenechloroarsenate, Ammonium 2-chloro-1-heptene-arsenate) is used for its tonic effects in various conditions such as anemias and malaria.



Chloroarsenol

Solarson is a one per cent solution of chloroarsenol in isotonic sodium chloride solution.

Lewisite (β -Chlorovinylchloroarsine). Lewisite (CHCl=CH—AsCl_2) is a vesicant and systemic poison used for chemical warfare. It has a geraniumlike odor. The first aid treatment involves its removal with sodium hypochlorite or hydrogen peroxide and treatment with BAL (British Anti-Lewisite) (See Chap. 17).

AROMATIC ARSENICALS

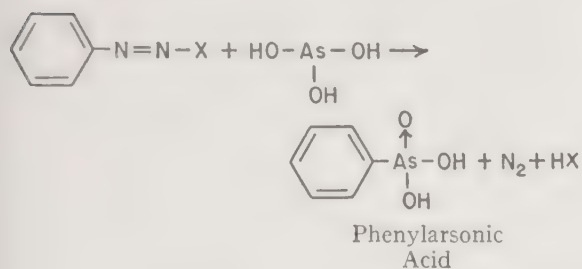
Several methods are available for preparing aromatic arsenicals.

1. BECHAMPS REACTION.

Other compounds with strong ortho-para

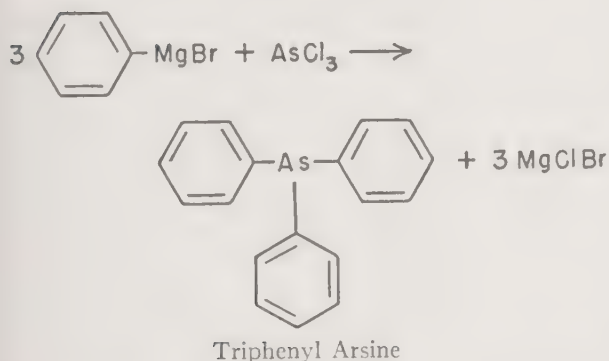
directing groups in the ring which can provide some activation react in a similar fashion, thus phenol can be arsonated.

2. BART REACTION.



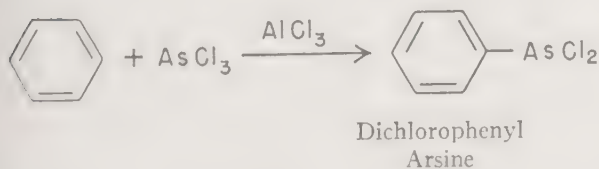
3. THE SCHELLER REACTION is a modified Bart reaction in which the reaction is carried out in absolute alcohol and an arsenous halide is used instead of arsenous acid.

4. GRIGNARD REACTION.



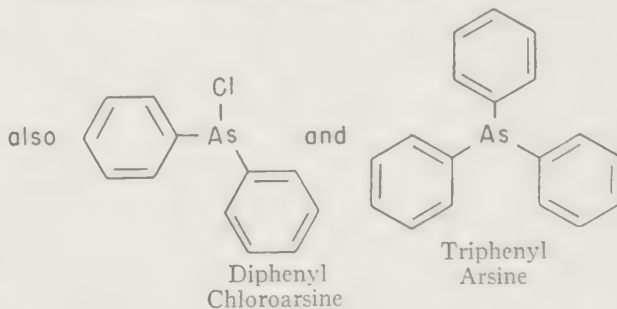
5. WIELAND (FRIEDEL-CRAFT) REACTION.

The most valuable arsenic compounds as therapeutic agents belong to the aromatic series. These compounds can be divided into



They became interested in arsonic compounds after Thomas, in 1905, used this acid therapeutically in the treatment of sleeping sickness and found it to be trypanocidal in vivo. However, it proved not to be active in vitro, a fact which Ehrlich accounted for by assuming that the inactive pentavalent compound was reduced to an active trivalent "arsenoxide" in the body.

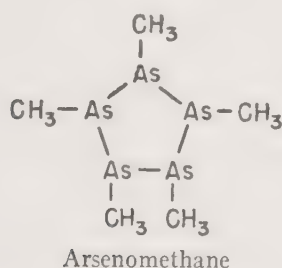
There are two types of trivalent arsenic compounds of therapeutic importance, the so-called "arsenoxides," which are also called arsenoso compounds and are thought to be characterized by the structure —As=O , and the arseno compounds, which are presumed to have the structure —As=As— . These structures were originally assigned because arsenoso compounds were considered analogous to nitroso compounds and arseno compounds were thought to be similar to the azo compounds. Structures of this type are to be found in standard books of reference including the U.S.P. and N.F. and in most text books of organic chemistry. It is possible, however, that such structures with an ordinary double bond attached to arsenic, antimony and bismuth are incorrect. Lewis,⁴ a number of years ago, proposed a rule that the ability to form ordinary double bonds (divalent bonds) is confined to elements in the first row of the periodic table, and it has been stated that no important exceptions to this rule have been found.⁵ Work⁵



three groups, one having arsenic in the pentavalent state and two having arsenic in the trivalent state. The first compound of this type studied was atoxyl which was prepared by Bechamp.² Ehrlich and Berthelm³ proved that it is *p*-aminobenzene-arsonic acid; they named it arsanilic acid.

on arsenomethane gives evidence that this compound does not have the structure $\text{CH}_3\text{—As=As—CH}_3$, but has single bonds between arsenic atoms. The structure that best fits the electron diffraction data is one with a five-membered ring. Other workers⁶ have

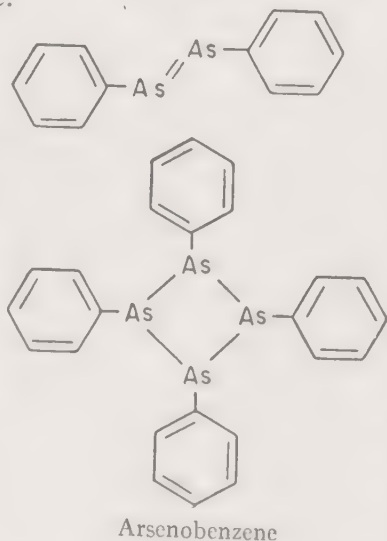
shown that compounds of the type $R-As=A$, where A represents two univalent radicals, are monomolecular in nonpolar solvents. However, if A is $=O$, $=S$ or $=NH$, the molecular weights are high, giving polymers represented by $(R-As=A)_n$, in which n is usually four but occasionally



two or three. The above facts, likewise, indicate that double bonds to arsenic are not present in these molecules, but suggest that the polymers have ring structures. Recent work⁷ on 3-amino-4-hydroxybenzene-arsinous acid (oxophenarsine, "arsenoxide") and derivatives gives evidence that certain single bond structures are more in keeping with the physical and chemical properties of the compounds than the $As=O$ structure.

Evidence that might be construed to be opposed to the view that arsenic cannot form double bonds is the finding that arsenobenzene has a very small or zero dipole moment.⁸ This was interpreted by the workers to mean that arsenobenzene is in the symmetrical trans form analogous to *trans* azobenzene.

However, a four-, five- or six-membered ring structure would also have a low or perhaps zero dipole moment and can just as well account for the experimental evidence.



That arsenic can form stable four-membered, single-bonded arsenic rings is shown by the structure of skutterudite⁹ $[Co_4(As_4)_3]$ in which the arsenic atoms have this arrangement.

More substantial evidence, from dipole moment data, that arsenic and some of the other atoms in rows beyond the first in the periodic table can form double bonds is given by the work of Phillips, Hunter and Sutton.¹⁰ The structures of many of the organo metallic compounds discussed in this chapter are not known with certainty and await further experimental evidence. In a number of cases, both the old double-bonded structure and a possible single-bonded analogue have been given.

The "arsenoxide" state is the form in which arsenic has the greatest therapeutic activity. This was not appreciated fully until Tatum and Cooper¹¹ in 1932 showed that oxophenarsine hydrochloride could be used in small doses for the effective treatment of syphilis. Before this much larger doses of pentavalent or trivalent arsenicals at the arsenobenzene oxidation level had been used, with the result that, while a small part of the arsenic in these compounds was converted to the effective "arsenoxide" state, the largest part stayed in the ineffective pentavalent or arsenobenzene state, serving to undermine the patient's health and comfort.

Although all arsenic compounds are quite toxic, sodium arsanilate and its derivatives seem to act with particular violence on the optic nerve, causing atrophy which results in blindness. In spite of the fact that the "arsenoxide" compounds are the most toxic, they are, in some respects, the safest to use because they are not converted to a more toxic compound in the body as is the case with either the arseno compounds or the arsonic acid derivatives. Thus, the arseno compounds can undergo oxidation, and the arsonic acids can be reduced to the "arsenoxide" state. The amount of these compounds converted to the most active and most toxic "arsenoxide" form is small, but

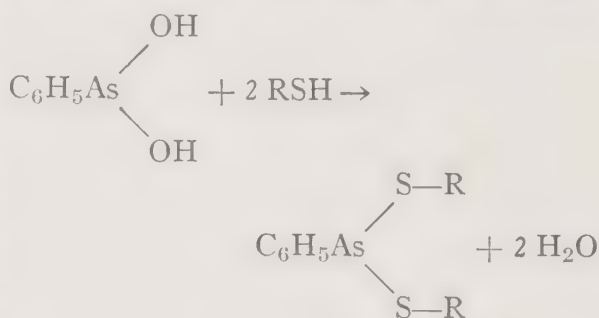
may vary with different individuals. Also, the arseno compounds, upon slight exposure to air, may be converted in part to the more toxic "arsenoxide" state. To insure the uniformity of some types of arsenicals, each lot must be released by the National Institute of Health before being offered for sale.

The pentavalent arsenicals have one advantage, however, they are highly mobile in the body, penetrating rapidly through all parts and, for the most part, being excreted unchanged. This great mobility makes the pentavalent compounds the most suitable for the treatment of neurosyphilis. The trivalent compounds are not effective for this since they fail to penetrate the central nervous system. Another condition where the pentavalent arsenical is favored is in amoebic dysentery, where a large arsenic concentration is desired in the stools.

Ehrlich made two brilliant guesses in regard to the therapeutic activity of arsenic, the first being that the pentavalent compounds were reduced to the active trivalent compounds in the body, the second being that arsenoxide compounds reacted with thiol groups in the organism. This has been well established by later workers,^{12,13,14} who demonstrated that the action of arsenic compounds could be nullified by the addition of thiol compounds, such as thioglycolic acid. The large number of thiol groups essentially uses up all the arsenic compound, leaving none or very little of it available to combine with the thiol groups in the organisms. The action of BAL as a detoxifying agent is dependent upon the reaction of its thiol groups with arsenic. About forty enzymes are known that are inactivated when their thiol groups are blocked. The action between an "arsenoxide" and a thiol compound can be demonstrated in the test tube. It involves the splitting-out of water, as indicated by the equation at the top of the next column.

An interesting question in regard to the action of arsenicals is this: since thiol groups are present both in the parasite and the host, how can the arsenical eliminate the parasite

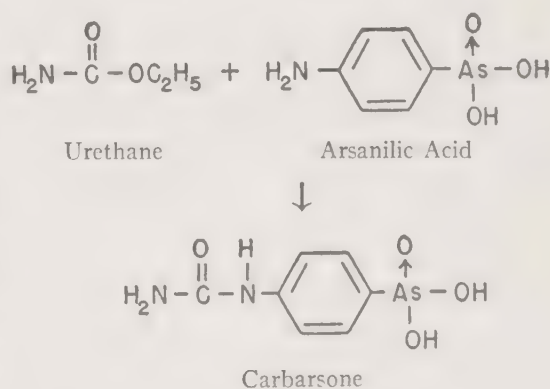
without eliminating the host? Several explanations have been suggested¹⁵ to account for this difference. The parasites may be able to concentrate the arsenical on or in their



bodies. At any event, it is well known that small organisms have a much higher metabolic rate than man, involving the consumption of roughly 200 times as much food per unit of body weight. This fact could, at least in part, account for the difference in the effect on the parasite as compared with the effect on the host.

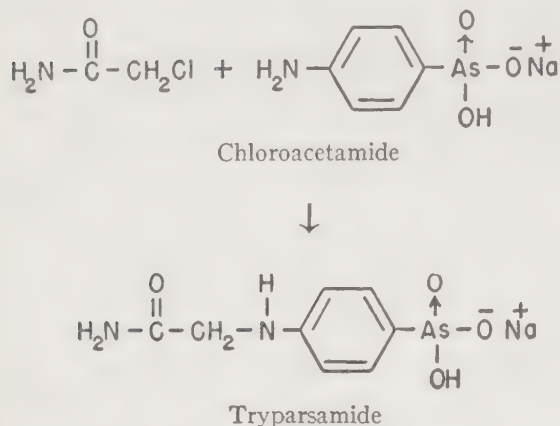
PENTAVALENT AROMATIC ARSENICALS

Carbarsone U.S.P. (*p*-Carbamidophenylarsonic Acid, 4-Ureido-1-phenylarsonic acid) occurs as a white, crystalline powder.



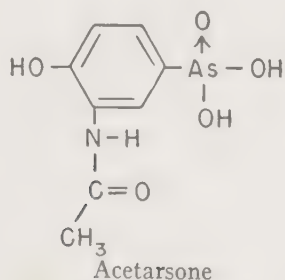
It is slightly soluble in water and alcohol, nearly insoluble in ether but soluble in basic aqueous solutions. It is used in the treatment of amebiasis, being administered orally. The average dose is 0.25 Gm.

Tryparsamide U.S.P. (Sodium *p*-arsenophenylglycineamide) is a white, odorless, crystalline powder, soluble in water (1:2), slightly soluble in alcohol and insoluble in



ether. It is used in the treatment of syphilis of the central nervous system and in the treatment of trypanosomiasis due to *T. gambiense*. The average dose is 2 Gm. by the intravenous route.

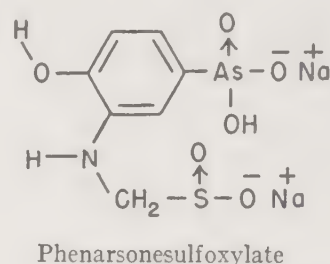
Acetarzone N.F. (Stovarsol, 4-Hydroxy-3-acetylaminophenylarsonic acid) is a white, odorless powder. It is slightly soluble in water, insoluble in alcohol but soluble in basic aqueous solutions. It can be made from *p*-hydroxyphenylarsonic acid by nitrating, reducing and then acetylating. It is used in the treatment of amebiasis, trichomonas vaginitis and sarcoid.



Acetylarsan (Diethylammonium-4-hydroxy-3-acetylaminophenylarsonate) is a 23.5 per cent aqueous solution of the diethylamine salt of acetarzone. It is recommended for the treatment of hepatic and cardiovascular syphilis. The dose is 2 to 3 cc. intramuscularly.

Treparsol (4-Hydroxy-3-formylaminophenylarsonic Acid), is similar in structure to Acetarzone, with a formyl group replacing the acetyl group.

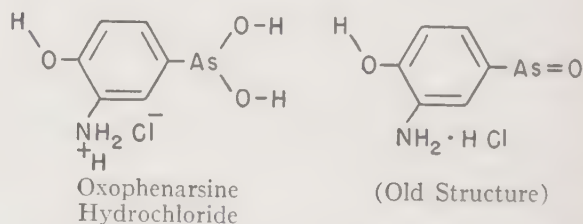
Phenarsonesulfoxylate (Aldarsone) N.N.R. [Sodium-3-amino-4-hydroxyphenylarsonate-N-methanal sulfoxylate, Sodium-3 (amino-N-methanal sodium sulfoxylate)-4-hydroxyphenylarsonate]. Phenarsonesulfoxylate is a white, odorless powder, soluble in water, slightly soluble in methyl alcohol and insoluble in ether and ethyl alcohol. It



is used in the treatment of trichomonas vaginalis vaginitis and syphilis of the central nervous system. The dose is 1 Gm. intravenously.

TRIVALENT ARSENIC COMPOUNDS

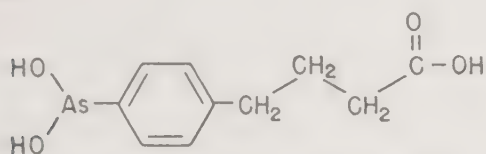
Oxophenarsine Hydrochloride U.S.P. (Mapharsen, 3-Amino-4-hydroxyphenylarsonoxidehydrochloride, 3-Amino-4-hydroxybenzenearsonous acid hydrochloride), is a white, odorless powder, soluble in water. It



is used in the treatment of syphilis, and the reactions following its use are said to be less severe than those accompanying the use of the arsphenamines. The compound is distributed as a mixture with buffers and other salts to make its solution isotonic and at a pH not damaging to tissue. It is interesting to note that this compound was made and tested years ago by Ehrlich but discarded because he found it very toxic. However, the important thing with any drug is not the inherent toxicity but the ratio of the therapeutic to the toxic dose and this ratio with

oxophenarsine hydrochloride was later found to be favorable. The average dose is 45 mg. intravenously.

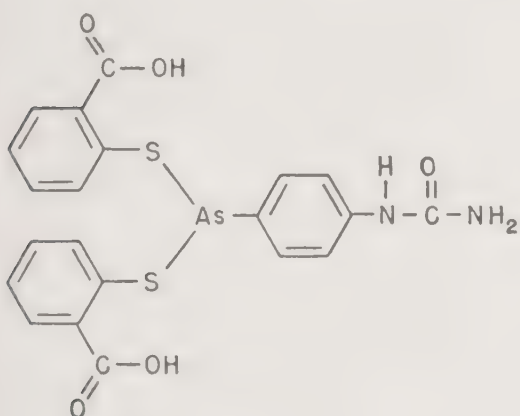
γ -(*p*-Arsenosophenyl)-butyric Acid is a stable, white, crystalline powder, slightly soluble in water and readily soluble in dilute alkali.



γ -(*p*-Arsenosophenyl)-butyric Acid

Neutral solutions of the sodium salt can be sterilized by autoclaving. It is active against "arsenic resistant" strains of trypanosomes such as *T. gambiense*. It appears to be an effective agent against African sleeping sickness.¹⁶ The dose is 0.3 mg. per kg. intravenously.

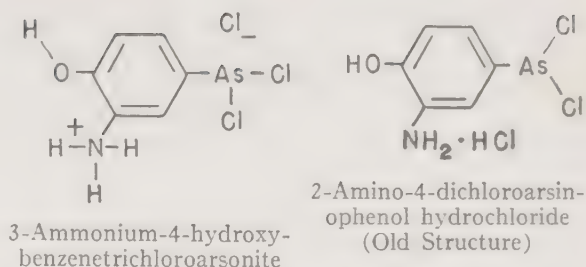
Anthiosen, C. C. #1037, *p*-[Bis-(*o*-carboxyphenylmercapto)-arsino]-phenylurea, is



Anthiosen

very slightly soluble in water, insoluble in dilute HCl, soluble in one normal NaOH (1:5) and soluble in alcohol (1:20). It is an effective amebicidal agent.¹⁷ The dose is 100 mg. three times daily after meals for seven days.

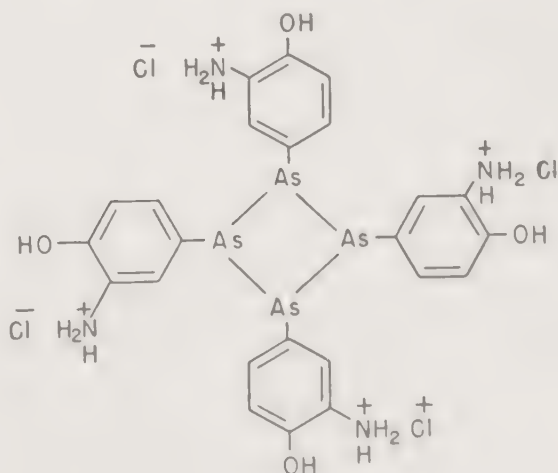
Dichlorophenarsine Hydrochloride U.S.P. (3-Amino-4-hydroxyphenyl-dichloroarsine hydrochloride, 3-Ammonium-4-hydroxybenzenetrichloroarsonite, Chlorarsen, Dichlor-mapharsen). Dichlorophenarsine hydrochloride is a white, odorless powder



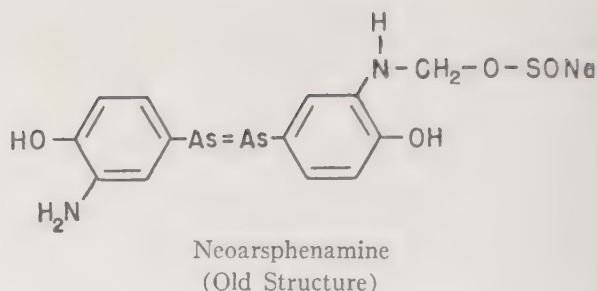
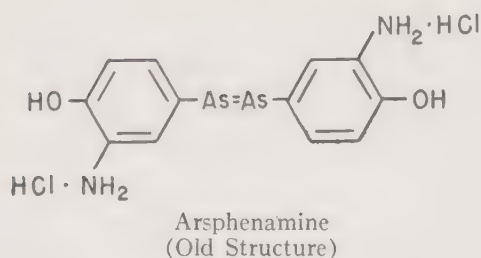
Dichlorophenarsine Hydrochloride

that is soluble in water. The compound is used in the treatment of syphilis and is another example of a compound that was tried years ago and discarded as being too toxic. The compound as originally used was not buffered, and consequently, the low pH had an added deleterious effect. At present, the preparations used contain enough buffer to make the solution about neutral for injection. The compound actually injected, however, consists in part, if not entirely, of the 3-amino-4-hydroxyphenylarsineoxide. This is produced from the rapid hydrolysis of the chlorine atoms attached to arsenic when water is added to the ampule containing the solid dichlorophenarsine hydrochloride and a solid buffer. The average dose is 45 mg. by the intravenous route.

Arsphenamine U.S.P. (3,3'-Diamino-4,4'-dihydroxyarsenobenzene dihydrochloride, Diarsenol, Salvarsan, 606) is a light-yellow, odorless, hygroscopic powder. It is soluble in water, alcohol and glycerin. The dry powder and its solutions are oxidized by



Arsphenamine



exposure to air, the resulting compounds being darker and more toxic. It is marketed in sealed glass containers with an inert gas such as nitrogen or is sealed under vacuum to prevent oxidation. The compound is acidic and is neutralized before use, each 0.1 Gm. of arsphenamine being treated with 0.85 cc. of normal NaOH. This is enough to convert both of the aminohydrochloride groups to the free amino groups and form the sodium salt with both phenol groups. The resulting solution has a pH of about 10.5 and hence is damaging to tissues.

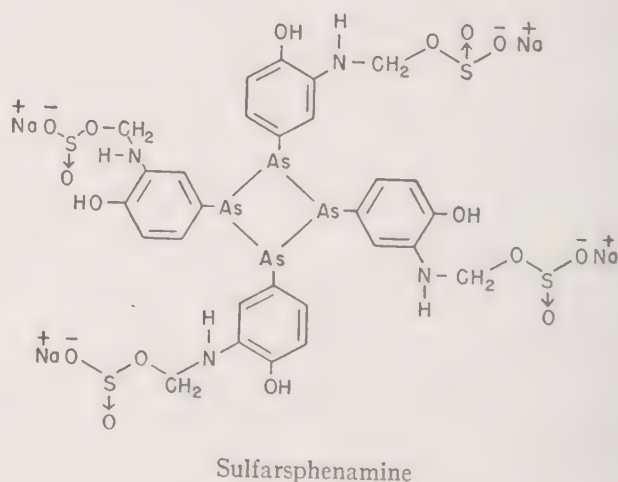
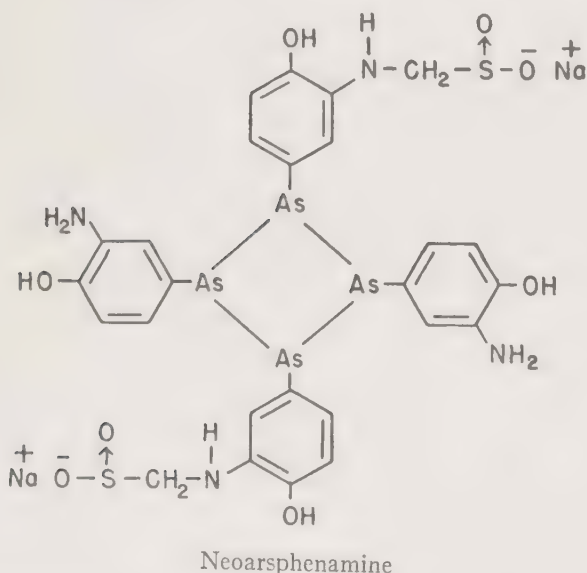
Arsphenamine is used in treating syphilis, relapsing fever and frambesia. The average dose is 0.3 Gm. intravenously.

Neoarsphenamine U.S.P. (Sodium 3,3'-

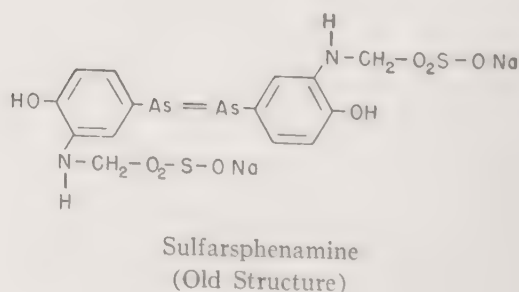
It is easily oxidized by air, both when in the solid state or in solution, and consequently, solutions being prepared for injection should not be heated or shaken and should always be freshly prepared. The drug should be kept in a refrigerator or in a cool dark room.

Neoarsphenamine is used for the same purposes as arsphenamine. It can be administered intramuscularly as well as intravenously, although the latter route is preferable. The dose is 0.45 Gm. intravenously.

Sulfarsphenamine U.S.P. (Disodium 3,3'-diamino - 4,4' - dihydroxyarsenobenzene - N-dimethylenesulfite or sulfonate) is a yellow powder that is very soluble in water, slightly soluble in alcohol and insoluble in ether. Its



diamino - 4,4' - dihydroxyarsenobenzene - N-methanal sulfoxylate, Neodiarsenol, Neosalvarsan, 914) is a yellow powder that is very soluble in water, soluble in glycerin and almost insoluble in absolute alcohol, ether and chloroform. Its water solutions are nearly neutral.

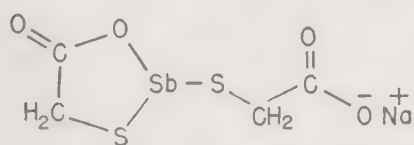


action and uses are much the same as those of neoarsphenamine. It is somewhat more stable in solution in the presence of air and it can be used more readily for intramuscular injection. There appear, however, to be more untoward reactions following its use than is the case with most other arsenicals used in treating syphilis. The dose is 0.45 Gm. intramuscularly.

Silver Arsphenamine (Sodium silver arsphenamine) is a compound whose exact structure is not known with certainty, but presumably the silver is attached to the amino groups in arsphenamine in much the same way that silver is attached to nitrogen in the silver-ammonium complex. It is readily soluble in water, giving a dark-brown solution that has an alkaline reaction. The presence of silver is said to improve the chemotherapeutic index of the compound because silver itself has an antisiphilitic effect. It is used for the same purposes as arsphenamine. The dose is 0.2 Gm.

ANTIMONY COMPOUNDS

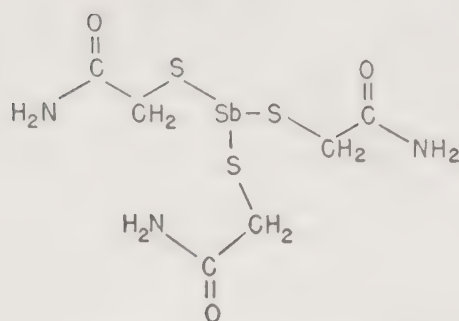
Antimony Sodium Thioglycollate U.S.P. is a white powder that is odorless or has



Antimony Sodium Thioglycollate

a faint mercaptanlike odor. It is freely soluble in water, is insoluble in alcohol and is decomposed and discolored by light. It is used in the treatment of schistosomiasis, leishmaniasis and granuloma inguinale. It is somewhat less toxic and less irritating than antimony and potassium tartrate. The intravenous or intramuscular dose is 50 mg.

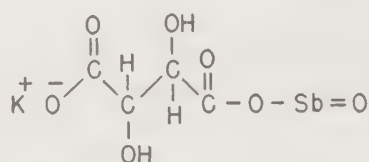
Antimony Thioglycollamide N.N.R. is a white, crystalline, odorless powder that is soluble in water (1:200), somewhat soluble in alcohol and insoluble in ether. It is used for the same purposes as antimony sodium thioglycollate and is somewhat more stable but also more toxic than the thioglycollate. The average dose is 0.08 Gm.



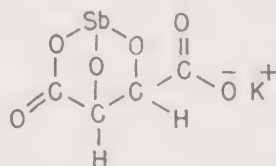
Antimony Thioglycollamide

Antimony Potassium Tartrate (Antimonyl Potassium Tartrate, Tartar Emetic) U.S.P. occurs either as colorless, odorless, transparent crystals or as a white powder, depending on whether or not the compound contains water of crystallization. The crystals effloresce when exposed to air. It is soluble in water (1:12), in glycerol (1:15) and is insoluble in alcohol.

The structure frequently given for antimony potassium tartrate is undoubtedly in-



correct. First, because antimony does not have any appreciable tendency to form double bonds and, secondly, because antimony, like bismuth, arsenic and some other metals, reacts with secondary alcohol groups. The structure proposed by Reihlen and Hezel overcomes this objection,¹⁸ but if one

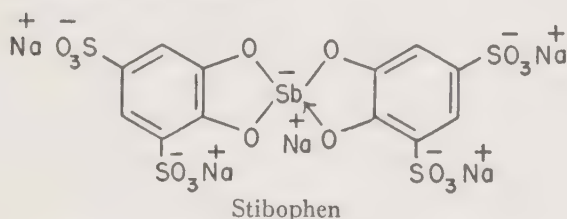


attempts to construct this molecule with the Fisher-Hirschfelder-Taylor models it is apparent at once that the second ring cannot be formed without greatly distorting the usual bond distances and angles. A more plausible structure is one in which the third valence of antimony is satisfied by an oxygen on a neighboring molecule or by a hy-

droxyl group. A dimer held together by an oxygen between two antimony atoms also may be a possible structure.

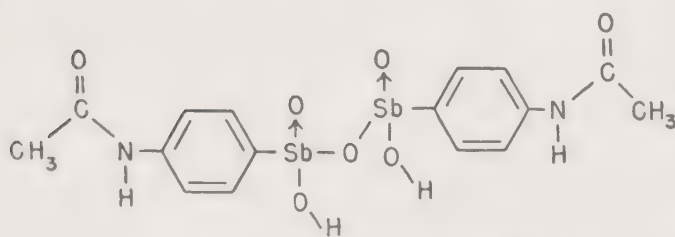
The compound is used orally as an expectorant and as an emetic. It is employed intravenously in the treatment of a number of tropical diseases including leishmaniasis, granuloma inguinale and sleeping sickness. The average oral dose as an expectorant is 3 mg. The intravenous dose is 30 to 150 mg.

Stibophen N.F. (Fuadin, Penta-sodium-antimony-bis-catechol-2,4-disulfonate) is a white, odorless, crystalline powder. It is freely soluble in water and nearly insoluble in alcohol and ether.



It is used in the treatment of schistosomiasis and granuloma inguinale. The compound is sensitive to light and should not be brought into contact with iron. The average dose is 0.2 Gm.

Ethylstibamine (Neostibosan) N.N.R. "A pentavalent antimony-organic complex mixture consisting of *p*-aminophenylstibonic acid, largely as a tetramer; *p*-acetylaminophenylstibonic acid, largely as a dimer; antimononic acid, and diethylamine in the approximate molecular ratio 1:2:1:3, respectively." Although these compounds are



Dimer of *p*-Acetylaminophenylstibonic Acid

called tetramers and dimers of substituted stibonic acids, they might more properly be considered as substituted stibonic acid anhydrides.

Ethylstibamine is used in the treatment of Kala-azar and dermal leishmaniasis. A five per cent solution is used for intravenous injection, and a twenty-five per cent solution for an intramuscular injection. Solutions should be used immediately and not heated. The dose is 0.2 Gm.

Stibamine Glucoside N.N.R. (Neostam) is a nitrogen glucoside of sodium *p*-aminophenylstibonate. The structure of the compound has not been elucidated completely, but provisionally a structure has been assigned to the compound in which three *p*-aminophenylstibonic acid molecules are linked together by anhydride linkages and three glucose molecules are attached to each amino group. It is used in the treatment of Kala-azar, and may be injected either intravenously or intramuscularly. The dose is from 0.05 to 0.3 Gm. per 100 lb. of body weight.

Lithium Antimony Thiomalate (Anthi-omaline) is said to be a specific for bilharziasis.

BISMUTH COMPOUNDS

Bismuth compounds may be divided into three classes. The insoluble compounds are used for their protective action on inflamed or irritated surfaces. These compounds are mildly astringent and antiseptic but their mechanical protective action and drying properties are of considerable importance. Some of the compounds are used entirely externally as dusting powder antiseptics but others are used both externally and internally for the treatment of such conditions as diarrhea and dysentery. The effectiveness of this type of compound is said to be associated in part with the fineness of the state of division of the compound.

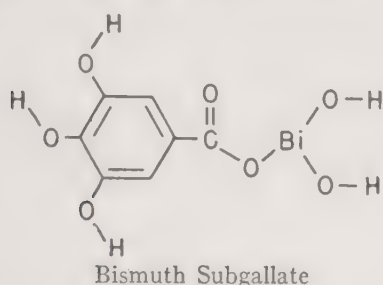
Water-soluble bismuth compounds are used for their trypanocidal and spirocheto-cidal action. These compounds have been used fairly extensively for the treatment of syphilis alone, or usually, in conjunction with arsenic therapy.

Oil-soluble bismuth compounds are used for the same purposes as the water-soluble

compounds. Bismuth is said to lie intermediate between arsenic and mercury as an antisyphilitic agent.

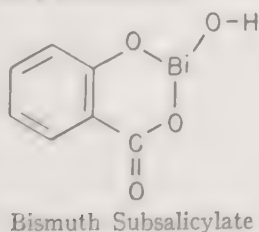
INSOLUBLE COMPOUNDS

Bismuth Subgallate (Basic Bismuth Gallate, Dermatol) N.F. is a bright yellow, odorless and tasteless powder that is stable in air but sensitive to light. It is insoluble in water, alcohol and ether but dissolves in bases and in warm, moderately strong solutions of mineral acids. A certain amount of decomposition accompanies its solution in these solvents. The composition of the substance is somewhat variable, giving from fifty-two to fifty-seven per cent of Bi_2O_3 on ignition. The structure given is one of several possible compounds that may be present.



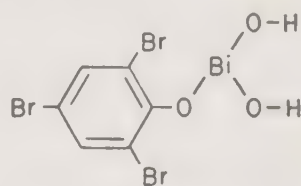
Others involve different amounts of hydration and a dimer or anhydride in which two molecules are linked through bismuth by an oxygen atom. The substance is used both internally and externally as an antiseptic and astringent protective. The average dose is 1 Gm.

Bismuth Subsalicylate (Basic Bismuth Salicylate) U.S.P. is a white, odorless powder that is stable in air but is affected by light. It is insoluble in water. The substance is of variable composition, giving from sixty-two to sixty-six per cent of Bi_2O_3 on ignition. It probably contains molecules of the structure given as well as dimers and hydrates of this structure.



It is used both externally and internally as an antiseptic and astringent protective. It is also used for its systemic effect in the treatment of syphilis, for which purpose it is injected as a suspension in oil. The oral dose for such conditions as diarrhea is 1 Gm. The intramuscular dose as an antisyphilitic is 0.1 Gm. in oil.

Bismuth Tribromophenate (Xeroform) N.N.R. is a yellow powder, insoluble in water and only slightly soluble in alcohol and chloroform. It is of somewhat variable composition but the structure given represents one of the possible components.

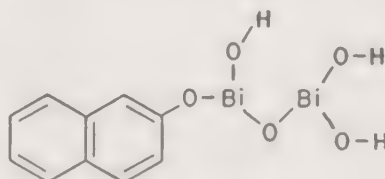


Bismuth Tribromophenate

It is used externally as an antiseptic dusting powder for the treatment of skin infections and internally in dysentery and similar gastro-intestinal conditions. The dose is 1 to 3 Gm. per day orally. For skin infections, ointments and lotions of from 3 to 10 per cent concentration are used.

Bismuth Formic Iodide (BFI Powder) is a mixture of formaldehyde, gelatin, thymol iodide and bismuth oxyiodide. It is used as an antiseptic powder like iodoform.

Bismuth β -Naphthol is a brown powder of faint aromatic odor that is very slightly soluble in water. It contains about seventy-five per cent Bi_2O_3 . A possible structure is given here.



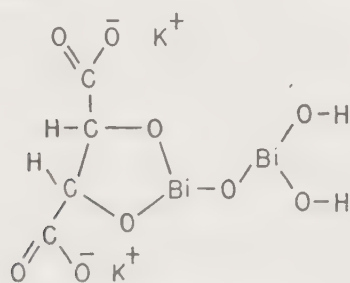
Bismuth β -Naphthol

The substance is used as an intestinal astringent and mild antiseptic in the treatment of dysenteries and diarrheas. The oral dose is 0.32 Gm.

Bismutose (Bismuth Albuminate) is a bismuth-albumin combination containing twenty-two per cent bismuth. It is a tasteless and odorless powder. It is used as a gastric antacid and as an intestinal astringent. The dose is 1 to 3 Gm.

WATER-SOLUBLE COMPOUNDS

Bismuth Potassium Tartrate (Potassium Bismuth Tartrate, Potassium Bismuthyl Tartrate) U.S.P. is a white, odorless powder that has a sweet taste and is sensitive to light. It is soluble in water (1:2) and is insoluble in alcohol, ether and chloroform. The substance is of variable composition, containing from sixty to sixty-four per cent of bismuth. A possible structure is the following:



Bismuth Potassium Tartrate

Bismuth potassium tartrate has been used in the treatment of syphilis but is little used at the present time. The dose is 0.1 Gm. intramuscularly.

Bismuth Sodium Tartrate N.N.R. (Sodium Bismuthyltartrate) is a white, odorless and tasteless powder that is soluble in water (1:3). It contains 72.7 to 73.9 per cent bismuth. It has the same use and general composition as the corresponding potassium salt. The dose is 30 mg. intramuscularly.

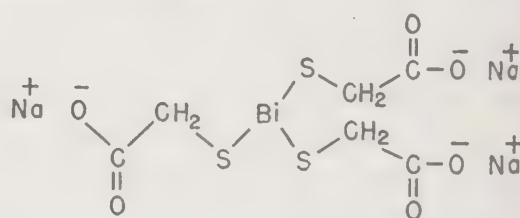
Potassium Sodium Bismuthyl Tartrate N.N.R. is a white powder, soluble in water and insoluble in organic solvents. It contains 40.75 to 41.25 per cent bismuth. Its composition must be considerably different from that of the bismuth potassium tartrate, which contains about 62 per cent bismuth. It is used to obtain the systemic effects of bismuth in the treatment of syphilis.

Bismosol is a solution containing 10 per cent of sodium potassium bismuthyltartrate and 0.3 per cent piperazine in an aqueous solution of glucose. It is used to obtain the systemic effects of bismuth. The dose is 1 cc.

Quinine Bismuth Iodide N.N.R. is a red powder that is almost insoluble in water and organic solvents. It is proposed for use to obtain the systemic effects of bismuth. The preparation Quiniobine is quinine bismuth iodide rendered soluble by the addition of lecithin.

Bismuth Suspension is a 2½ or 5 per cent suspension of quinine bismuth iodide in sterile olive oil with 3 per cent chlorobutanol. It is an antisyphilitic agent that is given intraglutarially but never intravenously because of the possibility of emboli formation or bismuth poisoning. The dose is 0.1 Gm.

Bismuth Sodium Thioglycollate (Thio-Bismol) N.N.R. is a yellow, hygroscopic, granular compound with a garliclike odor. It is freely soluble in water but the water solutions are unstable.



Bismuth Sodium Thioglycollate

It is used in the treatment of syphilis and is said to be absorbed readily, with the production of little local injury. The intramuscular dose is 0.2 Gm.

Sobisminol Mass N.N.R. is a red-brown, pasty material with an odor of triisopropanolamine. It has a bitter taste with a sweet metallic after-taste. It is soluble in ether and acetone. The water solution is highly basic. One gram in 10 cc. gives a solution with a pH above 11. It is obtained by the interaction of sodium bismuthate, tri-isopropanolamine and propylene glycol. The exact nature of the substance has not been established, but in view of known tendency of metals such as bismuth to react with secondary alcohol

groups, the product may contain structures analogous to those proposed for the co-ordination compounds of antimony-catechol with amines and alcohols.¹⁹ Sobisminol Mass contains 19.25 to 20.25 per cent bismuth. It is used for the treatment of syphilis by the oral route. Absorption of the substance is rapid and sufficient to give an effective antisyphilitic concentration of bismuth in the body. The average dose is 1.5 Gm.

Bisulfina is a solution containing approximately 1 per cent of bismuth and 6.5 per cent of sclero-sulphydryl proteins. It is used in the treatment of syphilis, either alone or in combination with arsenicals.

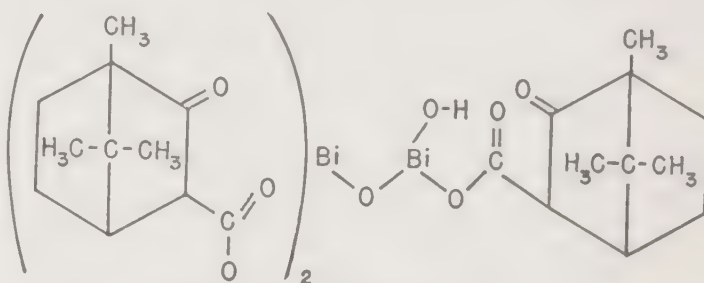
Bismuth Arsphenamine Sulfonate (Bismarsen) N.N.R. Sulfarsphenamine bismuth, is "the sodium salt of a bismuth derivative of arsphenamine methylene sulfonic acid (the exact structural formula of which has not been established) with inorganic salts." It is a brownish-yellow powder, readily soluble in water, giving a basic solution. The preparation contains approximately 24 per cent bismuth and 13 per cent arsenic. The substance is made from 3,3'-diamino-4,4'-dihydroxyarsenobenzene-*N,N'*-dimethylene sulfonate (sulfarsphenamine) and potassium bismuth tartrate by mixing their water solutions, dissolving the precipitate with sodium hydroxide, precipitating by pouring into methanol-ether, filtering and drying by vacuum.

It is used in the treatment of syphilis. As some pain may accompany the injection, it is usually given with butyn sulfate. The dose is 0.1 to 0.2 Gm. dissolved at the time of administration in 1 to 2 cc. of a sterile aqueous solution of 0.25 per cent butyn sulfate.

Sacbismuth is a solution of neutral potassium bismuth saccharate in aqueous sucrose with 2 per cent benzyl alcohol as a local anesthetic. Each cc. contains 0.05 Gm., equivalent to 0.025 Gm. of bismuth. It is used as an antisyphilitic. The dose is 1 or 2 cc. intraglutially.

OIL-SOLUBLE COMPOUNDS

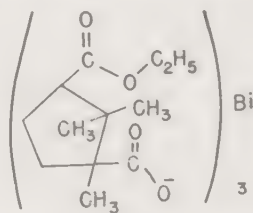
Bismuth Camphocarboxylate (Bismocymol) N.N.R. is a basic bismuth salt of camphor-3-carboxylic acid. It occurs as a white powder having an odor similar to camphor and is soluble in vegetable oils, ether and benzene, but is insoluble in water. The probable structure of the compound is the following:



Bismuth Camphocarboxylate

It contains from 37 to 40 per cent bismuth and is used in the treatment of syphilis. It is usually administered dissolved in olive oil. The dose is 0.1 Gm. intramuscularly.

Bismuth Ethylcamphorate N.N.R. is the bismuth salt of *d*-camphoric acid monoethyl ester. It occurs as a white solid with a faint aromatic odor. It is soluble in vegetable oils, ether and chloroform but is insoluble in water.



Bismuth Ethylcamphorate

It is used in the treatment of syphilis. The intramuscular dose is 2 cc. of a solution containing that quantity of the compound equivalent to 40 mg. of bismuth per cc.

Lipo-Bismol is a solution of bismuth acetyloxyacetate equivalent to 100 mg. of bismuth per cc. in an olive oil base together with 20 per cent benzylbenzoate. It is an antisyphilitic usually used in conjunction with an arsenical. The dose is 1 cc. intramuscularly.

Biliposol is a solution of basic α -carboxyethyl- β -methylnonate of bismuth in oil con-

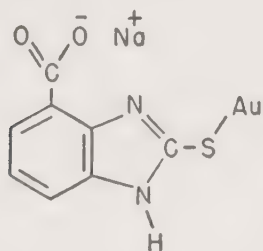
taining 40 mg. of bismuth per cc. It is used as an antisyphilitic for the treatment of arsenic-fast cases. The dose is 2 cc. intraglutiually.

Oleo-Bi-Roche is a finely-divided suspension of bismuth oleate in olive oil. It contains bismuth oleate equivalent to 0.05 Gm. of bismuth per cc. It is used in the treatment of syphilis. The dose is 2 cc. intramuscularly.

GOLD COMPOUNDS

Gold and its compounds have been used since early times in the treatment of various diseases, including syphilis, tuberculosis and cancer. They have not proved to be effective therapeutic agents, however, for these conditions. At present they are used for the treatment of lupus erythematosus and rheumatoid arthritis. Gold compounds are among the most toxic of all the metal compounds. Toxic manifestations involve skin, renal and hematologic reactions.

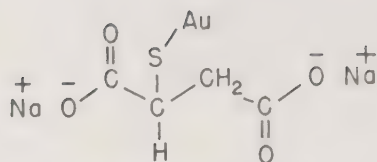
Triphal (Sodium aurothiobenzimidazol carboxylate) is a yellow powder, freely soluble in water. The water solutions are alkaline and decompose in a short time.



Triphal

The compound is used for the treatment of lupus erythematosus. The starting dose is 5 mg. and may be increased to 75 mg. It is administered intravenously.

Gold Sodium Thiomalate (Myochrysine) N.N.R. is a white or yellowish-white powder that is almost insoluble in alcohol and ether but very soluble in water. A 5 per cent aqueous solution has a pH of about 6. It is used for the treatment of rheumatoid arthritis. The dose is from 10 to 50 mg. intramuscularly.

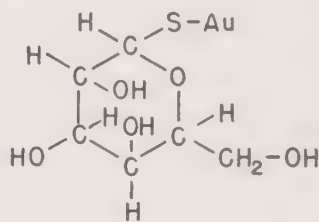


Gold Sodium Thiomalate

Krysolgan (Sodium 4-amino-2-aurothio-salicylate) has been used to some extent in the treatment of tuberculosis although it is not regarded as an effective agent for this disease.

Aurocein is a 5 per cent solution of a sulphydryl naphthyl derivative combined with gold and containing 0.5 per cent benzyl alcohol. It is given intramuscularly for the treatment of arthritis.

Solganol-B-Oleosum is a suspension of aurothioglucose in oil. Aurothioglucose is a water-soluble, oil-insoluble compound containing about 50 per cent gold.



Aurothioglucose

The preparation is used in the treatment of rheumatoid arthritis and lupus erythematosus. The dose is from 10 to 50 mg. intramuscularly.

TIN COMPOUNDS

A few tin preparations in which the tin is combined with an organic compound (usually a protein) have been proposed for the treatment of staphylococcal skin infections such as carbuncles and acne.

Chondro-Stann is a 6 per cent aqueous solution of sclero-sulphydryl protein combined with tin. The dose is 1 cc. intramuscularly.

Neostannin is a tin proteinate preparation in tablet form that is administered orally.

Staman is a colloidal tin proteinate with manganous gluconate put up in pulvoids for oral administration.

Stannine is a tin proteinate preparation in tablet form for oral administration.

Stanno-Yeast is a preparation of tin proteinate and brewers yeast in tablet form for oral administration.

Tinpronate is a preparation of tin combined with a protein base in tablet form for oral administration.

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19

Heterocyclic Compounds

FURAN
THIOPHENE
PYRROLE
PORPHIN DERIVATIVES
INDOLE
PYRAZOLE
IMIDAZOLE
THIAZOLE

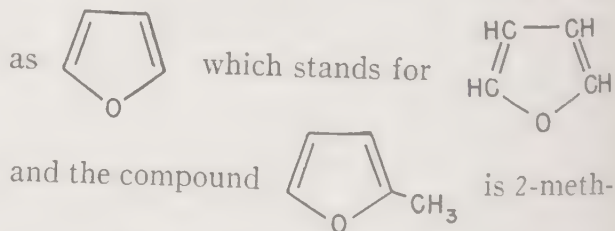
TRIAZOLES AND TETRAZOLE
OXAZOLE
PYRIDINE AND PIPERIDINE
QUINOLINE
DIAZINES—PYRIMIDINE
BARBITALS
PURINE
OTHER RING SYSTEMS

Heterocyclic compounds, as contrasted with homocyclic or isocyclic compounds, contain more than one kind of element in the ring. Up to the present we have considered the only important variety of homocyclic substances, carbocyclic or those composed solely of carbon. Theoretically, any one of the polyvalent elements could enter the ring in the place of carbon. Those heterocycles of pharmaceutical importance may be limited to compounds containing oxygen, sulfur and nitrogen.

Although it is possible to encounter rings containing any number of atoms from three up, as was the case in the homocyclic series, yet all important compounds here again have either five or six. We have only to deal, therefore, with the analogues of cyclopentane and cyclohexane, in which one or more of the carbon atoms has been replaced by oxygen, sulfur or nitrogen. Furthermore, as was found to be the case in the homo-

cyclic series, the most stable compounds are resonant, corresponding with cyclopentadiene and benzene.

In writing the formulas of these compounds, it is customary to use skeletons, indicating the hetero atoms and substituents only. The latter are shown as in aromatic compounds and designated in names by numbers, starting with the hetero atom as 1, or by Greek letters showing separation from the hetero atom. Thus, furan is given

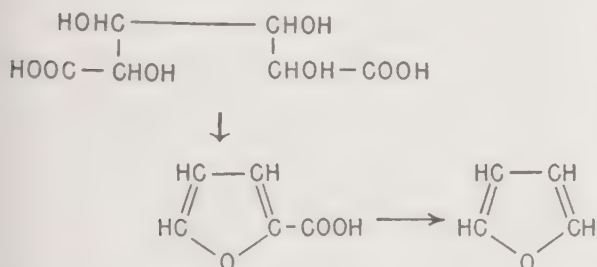


ylfuran or α -methylfuran. If there is more than one hetero atom, one of them is designated as 1 and the other cyclic atoms are counted so as to make the rest of the hetero

atoms have lowest possible numbers. The numbering of each ring system will be noted in its proper place.

FURAN

Furan or furfuran (from *furfur*=bran) occurs in wood tar and in the products of pyrolysis of many organic materials. It is a colorless liquid with a chloroformlike odor, is slightly soluble in water and boils at about 35° C. It gives a blue color with isatin and sulfuric acid, and its vapors give a green color with a pine splinter that has been moistened with hydrochloric acid. It can be prepared by heating barium hydroxide with the carboxyl derivative, which is itself a product of heating mucic acid.

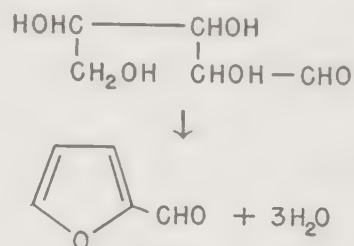


Furoic or pyromucic acid, the intermediate product, is a colorless, crystalline solid melting at about 133° C. and decomposing at about 275° C. to give furan and carbon dioxide.

Furfural (Furfurol), the corresponding aldehyde, is very important in commerce. It is a colorless, oily liquid that rapidly turns brown to black on standing, has an agreeable odor and boils at about 162° C. With reagents, it behaves very much as does benzaldehyde, including the Cannizzaro reaction, the formation of a phenylhydrazone and semicarbazone, and with potassium cyanide the production of furoin, which is analogous to benzoin. In aqueous solution, it gives a black precipitate with phloroglucinol; the precipitate can be filtered and weighed, a convenient method for the quantitative estimation of furfural, or pentosan from which it originates.

Furfural is manufactured in large quantities by heating any vegetable source of

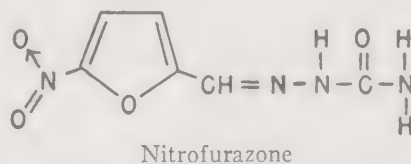
pentosans with dilute acid under pressure. The materials generally used are corn cobs or oat bran, but straw, wood, gums, etc., have enough pentosans to make the process economically profitable.



It is also formed during the pyrolysis of many vegetable materials and is, therefore, found in a large number of volatile oils, usually in the aqueous portion of the distillate because of its solubility (1:15) in water. Sometimes accompanying it in the oils are the 5-methyl derivatives and the corresponding alcohols of both, all of them probably having carbohydrates as their origin.

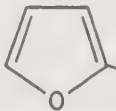
Furfural is employed in industry for a number of purposes. It is an excellent solvent for resins, for cellulose nitrates and acetates, and for gums. It also is used as a fungicide and insecticide, in paint removers, in the manufacture of synthetic resins of the Bakelite type, in shoe dyes and in rubber accelerators. The crude grade sells in quantity for about 10 cents a pound (1948).

Nitrofurazone (Furacin) N.N.R. is the semicarbazone of 5-nitrofurfural.



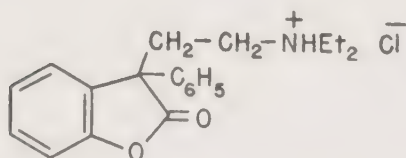
It is an odorless, tasteless, yellow crystalline solid that darkens on exposure to light. It is only slightly soluble in water, alcohol, ether or other common solvents, but dissolves more readily in propylene glycol or similar substance. The application of nitrofurazone in medicine followed the observation¹ in 1944 that furan derivatives containing a nitro group are bacteriostatic

and bactericidal. It seems to be effective against both gram positive and gram negative organisms, and is used chiefly for the treatment of ulcers of all types. In spite of the fact that it does not seem very toxic, a number of cases of sensitivity have been reported. It is recommended in 1:500 solution in carbowax 1500 and propylene glycol.

Furmethide, α -furfuryltrimethylammonium iodide, , is a

white, soluble, crystalline solid that is stable to light and is made by heating furfuryl iodide with trimethylamine. It has a chemical structure very similar to that of choline and, as might be expected, causes stimulation of the parasympathetic nerves with resulting myosis, fall in blood pressure, increased secretions and increase in intestinal peristalsis and contractility of the urinary bladder. It is recommended in atony of the bladder and the intestines after operation, using 5–8 milligrams subcutaneously or 10–30 milligrams by mouth, and in glaucoma² using 1 drop of a 10 per cent solution every 15 minutes for 2 hours, then every 3 hours until the tension is reduced to normal. Any untoward reactions, such as a precipitate fall in blood pressure or tachycardia, may be quickly and completely overcome by 0.6 milligram of atropine subcutaneously.

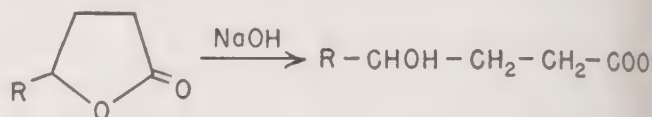
Amethone, 3- β -diethylaminoethyl-3-phenyl-coumaran-1-one hydrochloride, is rec-



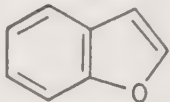
ommended for its antispasmodic action on smooth muscle in many organs, especially in the bladder and the ureter.³ It is employed⁴ to remove stones and relieve pain in cases of urinary calculi, to give relief in severe bladder spasms, catheterization and retrograde pyelography. It is much less toxic and mydriatic than atropine and has less

effect on the secretions. The dose is 0.1–0.15 gram intramuscularly before catheterization, 0.05–0.1 gram orally every 3 hours or 0.1 gram intramuscularly every 3 hours for passage of calculi.

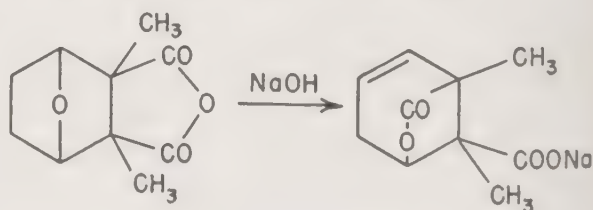
Many natural substances are derivatives of furan, although most of these, as is amethone, are γ -lactones whose rings are easily broken by alkalis to furnish salts of γ -hydroxy acids.



Some of the natural compounds are substitution products of coumarone or 2,3-benzo-

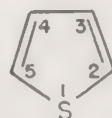
furan, , such as peucedanin

(q.v.). Cantharidin, the chief constituent of cantharides, is a more complicated compound, the anhydride of cantharidinic acid. When this is heated with alkalis, it is converted to a salt of cantharic acid.



THIOPHENE

This compound occurs in coal tar and is almost a constant impurity in commercial benzene, up to 0.6 per cent, because its physi-

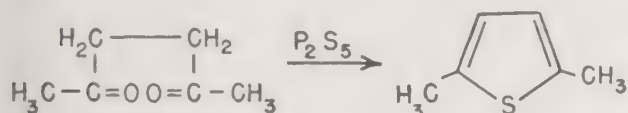


Thiophene

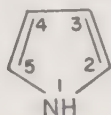
cal properties are like benzene in many ways; the odor is similar and the boiling point (84° C.) and specific gravity are about the same. The chemical behavior is also similar, although thiophene is somewhat more easily affected by some reagents. Benzene can be freed from this impurity by treating the mixture with sulfuric acid in

such a manner that only the thiophene is able to form a sulfonic acid; the thiophene can be regenerated from this by heating the lead salt with ammonium chloride. The usual method for purifying the benzene, however, is to treat it with mercuric oxide and acetic acid and subject it to distillation; thiophene forms a mercury compound that does not decompose or distil under these conditions. Just as do furan and pyrrole, thiophene gives a blue color with isatin and sulfuric acid, a reliable way to test for it in commercial benzene. This reaction was responsible for the discovery of thiophene in benzene in 1883.⁵

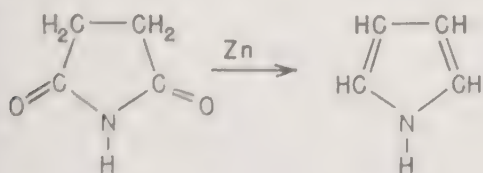
The derivatives are not very important, and they can be prepared in a number of ways. Thiophene itself is formed by heating barium furoate with barium sulfide, by heating sodium succinate or crotonic acid with phosphorus pentasulfide or by passing ethyl sulfide through a red-hot tube. By altering the reagents, alkyl and other substitution products can be produced; for example, 2,5-dimethylthiophene is obtained by heating acetonylacetone with phosphorus pentasulfide.



PYRROLE



This is found in coal tar and bone oil and in the products of distilling almost any vegetable or animal matter, such as in the volatile oils. Synthetically, it is prepared by heating ammonium mucate with glycerin, a method similar to that for furan or for thiophene, or by distilling succinimide with zinc dust.

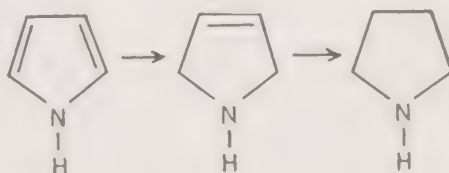


The dimethyl derivative is made by heating acetonylacetone with alcoholic ammonia, a method similar to that for dimethylthiophene.

Pyrrole is a colorless liquid that turns yellow to brown in the air, boils at 131° C. and has an odor similar to that of furan. It is only slightly soluble in water or alkalies, but is soluble in acids, in alcohol or in other organic solvents, and is a weak base. The nitrogenous hydrogen can be replaced in non-aqueous solution to yield a sodium or potassium salt. Halogens will substitute for the hydrogen in alpha position but will not add as they may in benzene, while nitric or sulfuric acids have no action. Sodium pyrrole with carbon dioxide under pressure produces α -pyrrolecarboxylic acid, a reaction that is analogous to the Kolbe synthesis of phenolic acids. With pine wood and hydrochloric acid, the vapors give a bright red color (pyrrole = fiery red). Like furan and thiophene, it gives a blue color with isatin and sulfuric acid.

Iodol or tetraiodopyrrole, $\text{C}_4\text{I}_4\text{NH}$, an insoluble, grayish-brown powder that is formed by the action of iodine in alcoholic solution, is sometimes used as a substitute for iodoform in surgical dusting powders, but is probably not effective. It has also been employed as a remedy in scrofula and tertiary syphilis, using doses of 0.15 to 0.3 gram.

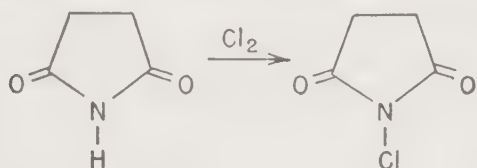
Reduction of pyrrole with zinc and acetic acid produces pyrroline, a base strong enough to form stable salts, and further reduction with stronger agents gives pyrrolidine, which is as strong as the aliphatic amines.



The nucleus of pyrrolidine is frequently a constituent part of the molecule in many natural compounds, especially in certain alkaloids. The amino acid proline is α -

pyrrolidinecarboxylic acid, and hydroxyproline (oxyproline) is 4-hydroxyproline.

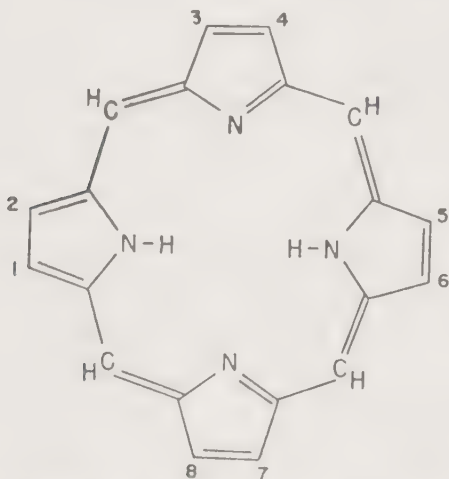
Succinchlorimide N.F. "contains not less than 25 per cent and not more than 27 per cent of active Cl." It consists of a white, crystalline powder with the odor and taste of chlorine. It is affected by light and dissolves in water (1:70) to give an acid solution. It is made by the direct chlorination of succinimide, which is 2,5-diketopyrrolidine.



It is used for the disinfection of water, as is halazone, in the proportion of 11.6 milligrams per liter.

PORPHIN DERIVATIVES

A number of vegetable and animal pigments contain a common structural pattern of four pyrrole nuclei bound together through methenyl carbon. Porphin, which may be regarded as the parent of these compounds, has the structural formula



and the others are derived by substitution in the eight beta positions. Protoporphyrin, which forms part of the molecule of hemoglobin in blood and which has been synthesized, has four methyl groups (1,3,5,8), two vinyl groups (2,4) and two $-\text{CH}_2-\text{CH}_2-\text{COOH}$ groups (6,7). Such porphyrins form N—metal compounds in which the

metallic element is closely associated electronically with all four nitrogen atoms. Protoporphyrin, thus combined with ferric iron, gives hemin and with ferrous iron heme, and if these are in turn combined with globin, they give oxyhemoglobin and hemoglobin respectively. Hemin, which contains one atom of iron to each molecule, has been produced synthetically, and its combination with the protein globin, previously made from hemoglobin, appears to be identical with the natural compound.

Hematoporphyrin, a red pigment that occurs in the body in certain pathologic conditions, can be produced by the action of dilute acid on hemin, thus removing the iron and otherwise altering the structure. It has been employed as a remedy in certain psycho-depressed conditions, but the results have not appeared to give any great promise. The substance is insoluble in water but dissolves in acids or bases to give a solution with a red fluorescence.

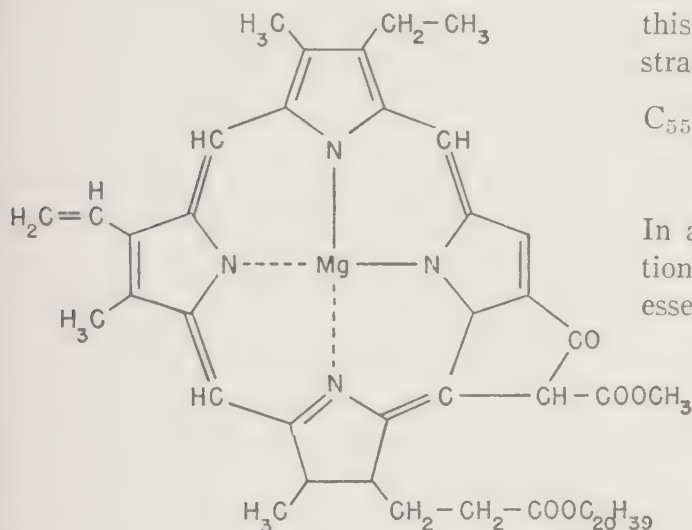
The biliary pigments, the most important of which are bilirubin and biliverdin, are not porphyrins, although they have the same porphin nucleus. They are probably oxidation products of hemoglobin.

Chlorophyll, the familiar green coloring matter of plants, is also a derivative of porphin that exists in two different forms, chlorophyll-*a*, $\text{C}_{55}\text{H}_{72}\text{N}_4\text{O}_5\text{Mg}$, and chlorophyll-*b*, $\text{C}_{55}\text{H}_{70}\text{N}_4\text{O}_6\text{Mg}$. The former is bluish-black in color and the latter dark green; neither is soluble in water, although they are soluble in alcohol, ether, acetone (with some water), chloroform or oils. They are separated in extractions by partition between benzin, which will dissolve *a* with difficulty, and methanol.

The exact structure of the chlorophylls is not known with certainty in spite of intensive research in the field for more than thirty years. The magnesium can be replaced by two hydrogen atoms to give pheophytins (*a* and *b*), and these can be hydrolyzed to phytol ($\text{C}_{20}\text{H}_{40}\text{O}$), methanol (CH_4O) and fundamental porphin derivatives with two

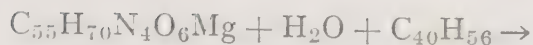
carboxyl groups ($C_{34}H_{34}N_4O_5$ and $C_{34}H_{32}N_4O_6$). In the first of these are four methyl groups, one ethyl group, one vinyl group, $-CH_2-CH_2-COOH$ and

$\begin{array}{c} O \\ || \\ -C-CH-COOH \end{array}$, while in the second, an aldehyde group takes the place of methyl in 1. The reconstructed formula that is at present accepted for *a* is



The position of the primary and secondary valence bonds between the atoms of nitrogen and magnesium and the consequent location of the double bonds in the pyrrole rings are subject to resonance and, therefore, not fixed; the formula given is but one of a number of arrangements for the double bonds.

The role of these substances in photosynthesis is probably definite but as yet not known with certainty, in spite of a vast amount of investigation. In the first place, the chlorophylls do not exist in the plants as such but are undoubtedly combined with some substances, either protein or lipid or both, since the isolated pigments have no influence on the synthesis. Furthermore, they are accompanied in the chloroplasts by carotenoid pigments, notably carotenes and xanthophyll, which seem to play a part. Baly and his co-workers⁶ postulate that chlorophyll-*a* is regenerated through action of carotene to produce xanthophyll.



The subsequent reduction of the last to carotene would permit the liberation of oxygen that is characteristic of the process. They also suggest that chlorophyll-*a* could react with the carbon dioxide to give a compound or compounds with the composition of formaldehyde, although the presence of this substance itself has not been demonstrated.



In any event, the chlorophylls or combinations of them with other substances seem essential to the photosynthetic process.

Unfortunately, a number of derivatives have been made that have also been designated as chlorophylls, including the pheophytins previously mentioned. When green leaves are extracted with ethyl or methyl alcohol instead of the usual acetone, the phytyl radical is displaced, through the influence of the enzyme chlorophyllase, by the smaller alkyl groups to give chlorophyllides, $C_{34}H_{33}N_4O_3MgCOOR$ and $C_{34}H_{31}N_4O_4MgCOOR$. Again, hydrolysis by sodium hydroxide gives sodium chlorophyllins, $C_{34}H_{31}N_4O_6MgNa_3$ and $C_{34}H_{29}N_4O_7MgNa_3$, that are called "water-soluble chlorophylls" and constitute the products that have been used in medicine; they are generally made from chlorophyll-*a*. The magnesium in these can be replaced to give copper or iron combinations that also have been employed.

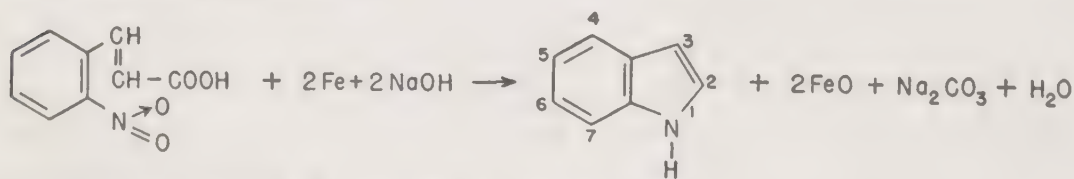
Since 1940, chlorophylls have been used locally in the treatment of various infections. The beneficial effects may be attributable partly to a mild antiseptic action, but they also appear to speed up the healing of wounds or abscesses by promoting development of new tissue. The literature gives several favorable reports⁷ on the treatment

of ulcers of all kinds, wounds, otitis media, sinusitis, skin diseases, burns, etc. The forms employed, usually of the water-soluble variety, are a 0.2 per cent solution in normal saline for irrigations, a 1 per cent ointment containing benzocaine and urea and a 0.5 per cent solution for nasal drops. Commercially available are preparations under the name Chloresium, an ointment and two solutions.

Chlorophyll also has been recommended in the treatment of anemias, partly on the basis of similarity in structure to hemoglobin and partly on pharmacologic observations. In recent years, the chlorophyllins of copper and iron have been suggested, but there does not seem to have been much attempt to exploit them commercially.

INDOLE

Indole, 2,3-benzopyrrole, (C_8H_7N) is found in coal tar, in the volatile oils of several flowers, including that of orange blossoms, and is partly responsible for the odor of fecal matter as a result of protein decomposition. It can be made synthetically in a number of ways, but is best produced by heating *o*-nitrocinnamic acid with iron powder and sodium hydroxide.



The product consists of colorless or yellow crystals with a strong fecal odor. It melts at 52°C . and boils at $253\text{--}254^{\circ}\text{C}$. with decomposition. Indole is soluble in hot water or organic solvents. It is a feeble base, as might be expected. With a pine shaving and hydrochloric acid, it yields a red color.

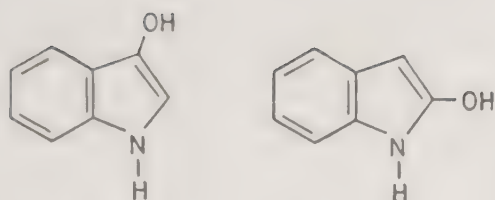
Several derivatives of indole are important in commerce or in the metabolism of plants and animals. Skatole, 3-methylindole, is found with the parent compound in coal tar, feces and oils. In spite of its fecal odor, it is very useful in perfumery as a blend. Indole-3-acetic acid, $C_8H_6N\text{--}CH_2\text{--}COOH$, and its homologues, indolepropionic

acid and indolebutyric acid, are used as growth hormones for plants or auxins. Tryptophane, α -amino- β -(3-indolyl)propionic acid or $C_8H_6N\text{--}CH_2\text{--}CH(NH_2)\text{--}COOH$, is one of the important amino acids from proteins, and is considered to be the precursor of indole and skatole in the feces. The corresponding α -methylamino compound is abrin, the toxic substance from jequirity seeds, *Abrus precatorius* L. Abrin has been used in a concentration of 1:500,000 for treating certain chronic diseases of the eye, but the method is probably too dangerous.

Progressive oxidation of indole produces a number of interesting substances, the final compound being either isatin or indigo. The first with mild agents is indoxyl, 3-hydroxyindole, which is an enol and undoubtedly exists also as the keto isomer. When indole is formed by putrefaction in the intestines, that which is absorbed is oxidized to indoxyl and detoxified by conversion to indican,* potassium indoxylsulfate, which is excreted in the urine. Oxindole or 2-hydroxyindole is also formed by mild oxidation of indole and also probably exists as a keto isomer. Either

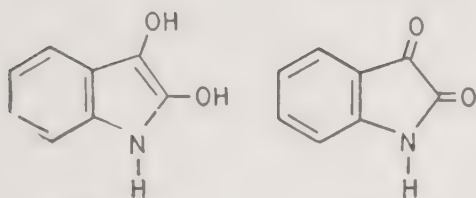
substance, as well as indoxyl, can be further oxidized to dioxindole, 2,3-dihydroxyindole or its tautomer 2-keto-3-hydroxydihydroindole. Nitric acid will convert indole or any of the other products to isatin, 2,3-diketodihydroindole, which is used as reagent with sulfuric acid to give a blue color with furan, thiophene or pyrrole. On the other hand, oxygen of the air, or better, ozone, will convert indole and the other substances to indigo, one of the most important of all dyes.

* Not to be confused with natural indican, a glycoside of indoxyl.



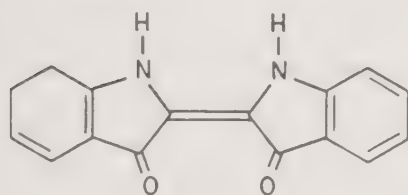
Indoxyl

Oxindole



Dioxindole

Isatin



Indigotin

Indigo (Indigotin, Indigo Blue) is a dark blue, odorless, tasteless powder that is insoluble in water. Formerly it was obtained from a glucoside indican, which occurs in a number of semitropical plants, particularly *Indigofera tinctoria* L., and which hydrolyzes to indoxyl and dextrose. Several synthetic processes are now available, but the one generally used converts aniline to phenylglycine, which in turn is fused with sodamide and sodium hydroxide to produce indoxyl. Nearly four million pounds are produced in the United States annually.

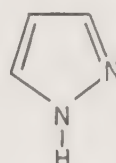
Indigo is used as a dye by the vat process. It is first reduced to indigo white or leucoindigo, which is colorless and soluble in alkalis. The textile is soaked in such a solution and then exposed to the air for reoxidation.

Sodium Indigotindisulfonate (Indigo Carmine) N.F. is made from indigotin by sulfonation. It consists of a dark, purplish-blue powder or blue granules with a coppery luster and is affected by light. It dissolves (1:100) in water, but is practically insoluble in other solvents. It is chiefly used in the laboratory as a coloring matter, stain or

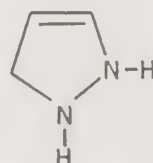
reagent. It is also injected as a test of kidney function, using 0.05–0.1 gram subcutaneously or intramuscularly or 8–16 milligrams intravenously. Normally, it appears in the urine in 10 minutes, and about 10 per cent of it is eliminated during the first hour.

PYRAZOLE

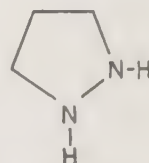
The simple compound containing two nitrogen and three carbon atoms in the ring, and with the nitrogen atoms neighboring, is known as pyrazole. The reduction products, named as are other rings of five atoms, are pyrazoline and pyrazolidine. Pyrazoline is of importance because it furnishes substitution products that are used in medicine. All of these may be referred to 5-ketopyrazoline or 5-pyrazolone, derived by making a compound that has a carbonyl group in position 5.



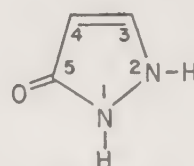
Pyrazole



Pyrazoline

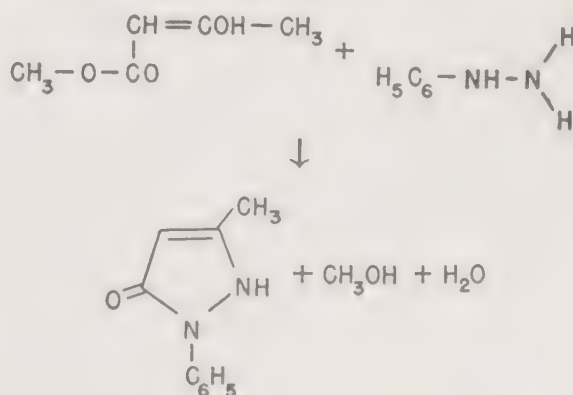


Pyrazolidine



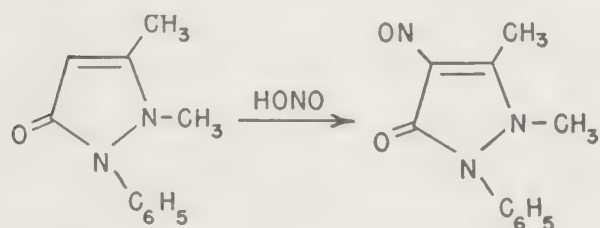
5-Pyrazolone

The preparation of these compounds depends upon condensation of hydrazine derivatives with various esters. Using phenylhydrazine and acetoacetic ester, 3-methyl-1-phenylpyrazolone is obtained.



The latter can be methylated by warming with methyl bromide to substitute the group in position 2, giving antipyrine. This will react with sodium nitrite and a dilute mineral acid to form 4-nitrosoantipyrine, and the latter easily can be reduced to the corresponding amine. Alkylation or acylation of this amino compound can produce a variety of substances, including the official aminopyrine. By using other hydrazines and different esters, a large number of compounds can be obtained, all of which are similar in physiologic action.

Antipyrine (Phenazone) N.F. also has been known by other names, for example, analgesine, anodynine, parodyne, phenylone and sedatine. It was one of the first important drugs to be made (1887) synthetically. It consists of colorless, odorless crystals or a white powder that has a slightly bitter taste and melts at 111–113° C. It is very soluble in water, alcohol or chloroform, less so in ether, and its aqueous solution is neutral to litmus paper. With ferric chloride, it gives a reddish orange color; with vanillin and sulfuric acid, an orange precipitate and with sodium nitrite and dilute sulfuric acid, a green color of nitrosoantipyrine.



It is incompatible with tannic acid, with which it gives a white precipitate; with some of the other alkaloidal reagents, notably potassium mercuric iodide, mercuric chloride and iodine; with calomel which it changes partly to mercuric chloride and mercury and with copper salts. Furthermore, it forms soft eutectic mixtures with acetanilid, salol, chloral hydrate, β -naphthol, etc.

Locally, antipyrine exerts a paralytic action on the sensory and motor nerves, resulting in some anesthesia and vasoconstriction, and it also exerts a feeble antiseptic

effect. Systemically, it causes results that are very similar to those of acetanilid, although they are usually more rapid. It is readily absorbed after oral administration, circulates freely and is excreted chiefly by the kidneys without having changed chemically. Any abnormal temperature is rapidly reduced by an unknown mechanism usually attributed to an effect on the hypothetical heat-regulating center of the nervous system. It also lessens perception to pain of certain types without any alteration in the mentality or motor functions, hence differs from the effects of morphine. Very often it produces unpleasant and possibly alarming symptoms, even in small or moderate doses. These are giddiness, drowsiness, cyanosis, great reduction in temperature, coldness in the extremities, tremor, sweating and morbilliform or erythematous eruptions; with very large doses there are asphyxia, epileptic convulsions, and collapse. Treatment for such untoward reactions must be symptomatic. It is probably less liable to produce collapse than acetanilid and is not known to bring the granulocytopenia that sometimes follows aminopyrine.

Antipyrine is employed in medicine less often in recent years than formerly. It is administered orally to reduce pain and fever in neuralgia, the myalgias, migraine, other headaches, chronic rheumatism and neuritis, but is less effective than salicylates and more toxic. It sometimes is employed in motor disturbances, such as the spasms of whooping cough or epilepsy. Occasionally it is applied locally in 5–15 per cent solution for its vasoconstrictive and anesthetic effects in rhinitis and laryngitis and sometimes as a styptic in nosebleed.

The great success of antipyrine in the early years led to the introduction of a great many derivatives, especially salts with a variety of acids, but none of these has any advantage over the parent compound. Among these might be mentioned the salicylate (Salipyrine), the acetylsalicylate (Acetopyrine), the valerate, the mandelate (Tus-

sol), the β -naphtholate, the ethylmethylglycollate (Astrolin) and the compound with chloral hydrate (Hypnal).

Aminopyrine (Amidopyrine) U.S.P., also marketed as Pyramidon, is 2,3-dimethyl-4-dimethylamino-1-phenyl-5-pyrazolone. It consists of colorless, odorless crystals that melt at 107-109° C. and dissolve in water and the usual organic solvents. It can be distinguished from antipyrine since it gives a bluish-violet color with ferric chloride, a violet color with silver nitrate, a dark blue color or precipitate with potassium ferri-cyanide and no color at all with vanillin and sulfuric acid. It has about the same incompatibilities but particularly gives a violet to yellow or brown color with mucilage of acacia, which can be prevented by heating the latter to destroy its oxidase before mixing. The crystals of aminopyrine are affected by light and must be stored in light-resistant containers.

It is employed as antipyretic and analgesic just as antipyrine but is somewhat slower in action. However, it seems to be much more powerful and its effects last longer; indeed, some authorities claim that it is just as effective as the salicylates in rheumatic fever and even maintain that it is practically specific. It has been used as routine treatment for measles, and is considered by some as the best agent for affording relief in diabetes insipidus, where it lowers the urinary output if not administered repeatedly. The dose is usually 0.3 gram for headaches, dysmenorrhea, neuralgia, migraine, etc., and it is often given several times daily in rheumatism and other conditions that involve continuous pain.

One of the chief disadvantages of therapy by aminopyrine is the possibility of producing agranulocytosis or granulocytopenia. Kracke⁸ showed that this is caused by drug therapy with a variety of substances, including mostly aromatic compounds, but particularly with aminopyrine; indeed, a number of fatal cases have been traced definitely to this drug. The symptoms are a marked fall in leukocytes, absence of granu-

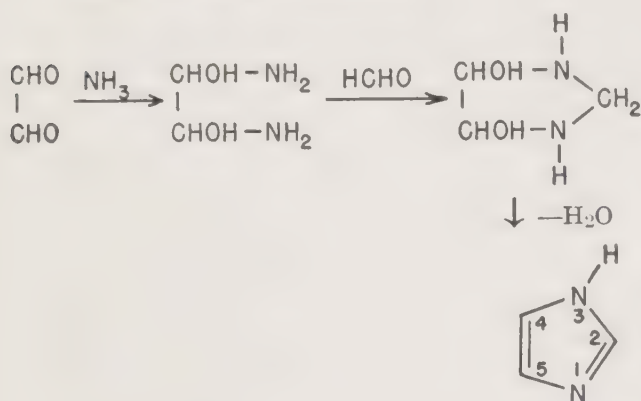
locytes in the blood, fever, sore throat, ulceration on mucous surfaces and prostration, with death in the majority of cases from secondary complications. The treatment is merely symptomatic, with penicillin to prevent any possible superimposed infection. The condition seems to be more or less an allergenic reaction because only a certain small percentage of those who use the drug are affected, but great caution must be observed to avoid susceptibility, and many countries have forbidden or greatly restricted its administration.

Larodon or 4-isopropylantipyrine is a white crystalline powder with a slightly bitter taste; it is sparingly soluble in water but more soluble in alcohol. It is claimed to be about twice as powerful as aminopyrine and to have a marked spasmolytic action on unstriated muscles. The recommended dose is 0.3 to 0.6 gram.

Several other derivatives of pyrazole may be encountered in pharmacy and in the laboratory. Melubrin is made by warming aminoantipyrine with formaldehyde and sodium bisulfite to give the group $\text{—NH—CH}_2\text{—SO}_3\text{Na}$ in position 4. It has been given in the same conditions as other drugs of the class in doses of 0.5 to 10 grams orally or 2.5 to 3 grams intravenously. Its N-methyl substitution product was marketed as Novalgin, Dipyron or Novaldin for the same purposes, and in the same class is Tolpyrine, which is made by using tolyhydrazine in place of phenylhydrazine in the manufacture. Iodopyrine (Iodoantipyrine, Antipyrine Iodide), containing more than 40 per cent of iodine, has been used as a substitute for the iodides in rheumatism, asthma and syphilis in doses of 0.3-1.0 gram and also like the parent compound as analgesic and antipyretic. There should also be mentioned the official reagent picrolonic acid, which is 5-hydroxy-3-methyl-4-nitro-1-*p*-nitrophenylpyrazole, and tartrazine (hydrazine yellow), one of the allowable colors, which is 5-hydroxy-4-*p*-sulfo benzeneazo-1-*p*-sulfo phenylpyrazole-3-carboxylic acid, trisodium salt.

IMIDAZOLE

Imidazole, an isomer of pyrazole, can be made from glyoxal and therefore, is also called glyoxaline. The synthesis involves treating the ammonia derivative with formaldehyde and dehydrating.

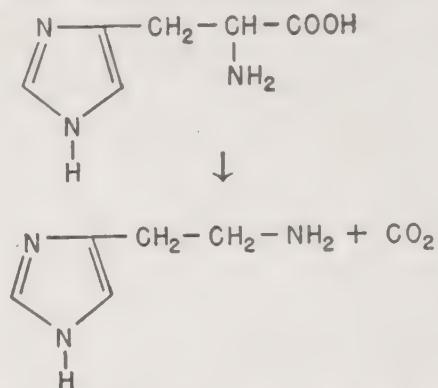


Reduction, as with other resonant compounds of the nitrogen heterocycles, gives imidazoline and imidazolidine. It is to be noted that all of these compounds have the nucleus of urea and that several syntheses are based upon reaction with this compound. It must also be observed that, because of the resonant shifting of double bonds, substitution in either of the positions 4 or 5 in imidazole gives rise to the same compound.

Histamine Phosphate (Histamine Acid Phosphate) U.S.P. is the acid phosphate of 4-(β -aminoethyl)imidazole with the formula $\text{NH}_2-\text{CH}_2-\text{CH}_2-\text{C}_3\text{H}_3\text{N}_2$ with $2\text{H}_3\text{PO}_4$, hence probably a diprimary phosphate. It occurs as colorless, odorless, long, prismatic crystals that melt at about 130°C . and dissolves readily in water to produce an acid solution. It is stable in the air but is affected by light. With phosphotungstic acid it gives a precipitate than can be used for quantitative estimation, with picrolonic acid it gives a precipitate that melts at $265\text{--}268^\circ\text{C}$. and with nitrous and sulfanilic acids it gives a deep red color.

Histamine occurs in ergot and other plants and is found in all organs and tissues of the body in very small amounts, being most concentrated in the lungs. It is prepared from citric acid through diaminoacetone,⁹ but the

most interesting method, because it is a process that probably takes place in the body, is from histidine by decarboxylation.



Outside of the body this can be brought about by a variety of conditions, such as by heat in the presence of acid or by the aid of ultraviolet light, while in the system it is effected by an enzyme, histidine decarboxylase, and in the intestines during putrefaction by some bacteria of the *E. coli* group.

The physiologic action of histamine is apparently complex and not well understood, chiefly because various species of animals often give entirely different results. Very little is absorbed from the gastrointestinal tract, even after large doses, but after the administration of small doses parenterally there are intense but variable reactions. There seems to be a stimulation of all smooth muscles, most evident in the uterus and bronchi, a lowering of blood pressure similar to that from shock and not cardiac or central in origin, and an increase in many secretions and in capillary permeability. The general picture is perfectly analogous to that from surgical or traumatic shock and to those of anaphylactic reactions, and most evidence makes almost inescapable the conclusion that sudden liberation of histamine from some combination may be responsible for shock, anaphylaxis and many allergic reactions. What is combined with it normally that prevents the usual effects is not known.

The use of histamine as a remedial agent is rendered very difficult because the effects are so variable and often result in dangerous or uncomfortable conditions. Attempts have

been made to use injections for desensitizing against allergic manifestations, especially in physical and other allergies, histamine cephalgia, Meniere's disease, migraine, etc. The results have been inconclusive, which leads to the inference that the compound is not antigenic. The further attempts to combine it with various proteins in order to create antigens, especially with despeciated horse-serum globulin (Hapamine), were successful in producing antibodies, but the clinical results were not very encouraging. The wheal caused by intradermal injection of a 1:1,000 solution has been suggested as a diagnostic test of local circulation; in normal individuals, the wheal appears in about 2.5 minutes, and any delay is considered as a sign of vascular disease. It also is suggested that, because it dilates the blood vessels, it could be used for the relief of myalgia, especially if administered by iontophoresis. For this purpose, the positive gauze-pad is moistened with a 1:5,000 solution, or a 2 per cent ointment is placed under the pad which is saturated with normal saline, and a current of 5-15 milliamperes is applied for from 5 to 30 minutes.

The chief use of histamine, however, is to diagnose impairment of the gastric ability to produce acid. Normally, it is the most powerful stimulant that is available, and absence of acid after injection is considered proof that the acid-secreting glands are damaged, a condition that is symptomatic particularly of pernicious anemia. The test is conducted by injecting 0.5-1.0 milligram in the form of a 1:1,000 solution in the fasting patient who has just previously taken a glass of water. Acidity in the gastric contents, aspirated every 15-20 minutes, then is determined in the usual way. Epinephrine will counteract the occasional untoward reactions such as headache and dizziness.

Because desensitization therapy was not particularly effective in allergies, attempts have been made to provide antihistaminic drugs. Naturally, the first experiments were with histaminase, which is present in tissues and is known to inactivate histamine in the

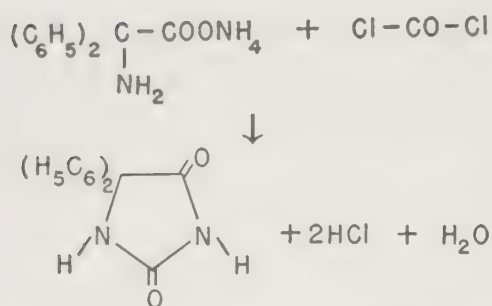
body. Preparations of this enzyme, such as Torantil, are available but have proved disappointing, probably because histaminase is inhibited or actually destroyed before the site of action can be reached. The use of epinephrine, atropine or other compounds that are known to counteract the effects of histamine was contraindicated because of deleterious side effects. In 1937, however, an intensive, systematic and successful study was begun to find compounds that are antagonistic and harmless. This field, which is being pursued actively in all parts of the world in 1948, has already produced benadryl, pyribenzamine, neoantargan, thenylene and many other promising agents, all of which will be described in the proper place. The experimental criteria of effectiveness are: reduction of bronchial constriction in guinea pigs previously exposed to atomized solutions of histamine or subjected to anaphylactic shock, suppression of the fall in blood pressure in dogs after injection of histamine and prevention of spasmogenic effects from barium or acetylcholine on intestines of the guinea pig.

OFFICIAL OCCURRENCE	PER CENT HISTAMINE PHOSPHATE
U.S.P.	
Histamine Phosphate Injection	0.1

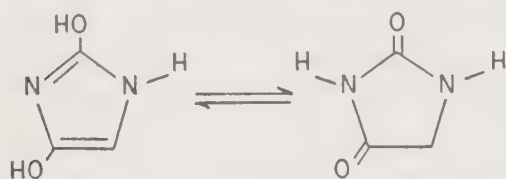
Histidine, of which histamine is a decarboxylated product and which is one of the essential amino acids, will be described in the chapter on proteins.

Diphenylhydantoin Sodium (Soluble Phenytoin) U.S.P. was originally introduced as Dilantin Sodium. It is a white, hygroscopic, odorless powder that dissolves readily in water to give an alkaline solution; it also dissolves in alcohol. It is incompatible with acids because they precipitate diphenylhydantoin, which melts at 292-299° C.

Diphenylhydantoin may be prepared by heating together potassium cyanide, ammonium carbonate and benzophenone in alcoholic solution or by condensing phosgene with the ammonium salt of aminodiphenylacetic acid.



The parent substance, hydantoin, is made by the condensation of urea and an ester of glycollic acid and, like any amide, can tautomerize to the enolic form.



The latter is obviously 2,4-dihydroxyimidazole, hence also the former, and diphenylhydantoin is 2,4-dihydroxy-5,5-diphenylimidazole.

The compound was selected as the most effective of a series to be used for anticonvulsant action, especially in epilepsy. While the mechanism by which it brings about such an effect is not known, it is presumed to act in a manner similar to phenobarbital. It is apparently more effective in seizures of the grand mal type. Various untoward effects have been observed; these include dizziness, skin rashes, itching, tremors, fever, vomiting, blurred vision, difficult breathing and hyperplasia of the gums. The last suggests deficiency of vitamin C, although diphenylhydantoin does not seem to interfere with utilization of ascorbic acid. The dose is 0.1 gram with plenty of water three times daily, but the amount must be determined by results and often may be increased gradually. For children under four years of age the starting dose is 0.03 gram mixed with cream or other agent to disguise the taste and prevent gastric irritation. The transition from phenobarbital or other drugs must be made gradually, with overlapping doses in order to eliminate the withdrawal symptoms of increased seizures.

OFFICIAL OCCURRENCE

U.S.P.

Diphenylhydantoin Sodium Capsules

Nirvanol or ethylphenylhydantoin was introduced in 1919 as hypnotic and sedative because of its similarity to the barbitals, but has more recently been used as a remedy in chorea. In the dose recommended (0.3 to 1.0 gram) it gives a stuporous state followed by toxic manifestations, including skin eruptions, fever and eosinophilia. These effects are presumed by many to be part of the cure, but Schick and Sobotka¹⁰ claim that the dextro variety gives remedial action without the toxicity.

Mesantoin (Phenantoin), 5-ethyl-3-methyl-5-phenylhydantoin, differs from nirvanol in having a methyl group on the nitrogen. It was introduced for grand mal seizures and is claimed to be more effective and less toxic. Untoward reactions, consisting of drowsiness and a skin rash, are encountered in about 10 per cent of the cases. The dose recommended is 0.2-0.6 gram daily, increased to 0.8 gram or more if necessary, and 0.1-0.4 gram for children.

Allantoin (Cordianine), the ureyl derivative of hydantoin (having the group $\text{NH}_2-\text{CO}-\text{NH}-$ in position 5), is a white, crystalline powder that is sparingly soluble in cold water but readily soluble in hot water. It can be prepared by the oxidation of uric acid with potassium permanganate or with the enzyme uricase, which is found in most animals but not in man. It also can be prepared by the condensation of urea with glyoxylic ester.

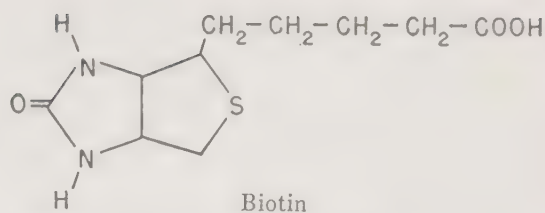
The application of allantoin in medicine followed the use of fly maggots. During World War I it was noted that osteomyelitic abscesses and severe wounds healed faster after being infested with maggots, and these maggots were cultivated commercially for the purpose of treating such conditions. Later allantoin was found to be present in extracts of the larvae and was recommended as a substitute for the purpose of stimulating cell proliferation in sluggish wounds, especially in osteomyelitis. Still later it was

suggested that the effective agent is urea, which is part of the molecule, and since then the employment of allantoin for the purpose has gradually decreased. It is applied as a 0.4-2.0 per cent solution, frequently combined with antiseptics, urea and sulfa drugs. It also has been recommended in doses of 0.03-0.13 gram for gastric ulcers and has practically no toxicity under such conditions.

Naphazoline Hydrochloride (Privine Hydrochloride) N.N.R., the salt of 2-(1-naphthylmethyl)imidazoline, is a white, odorless, crystalline powder that dissolves freely in water or alcohol, the aqueous solution having an acid reaction. Systemically, it raises blood pressure in a manner similar to that of epinephrine, but it is poorly absorbed from mucous membranes. Locally, it acts as a vasoconstrictor and causes a prolonged reduction of swelling and congestion. It is considered of value in the relief of disorders of the upper respiratory tract, such as nasal congestion of allergic or inflammatory origin, acute and chronic rhinitis, vasomotor rhinitis and acute and chronic rhinosinusitis. As with similar agents, care must be exercised to guard against rebound congestion in those persons who are peculiarly sensitive and get remedial effects with much smaller amounts.

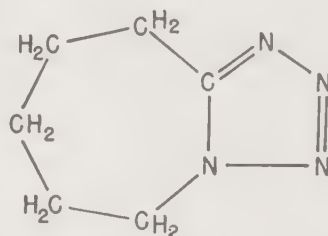
The method of employment calls for application of one to several drops of 0.05-0.1 per cent solution, depending on individual sensitivity; the effect lasts for several hours. The solution is buffered to a pH of 6.2-6.3 but may occasionally cause a smarting sensation or sneezing. A nasal jelly is also available.

Biotin, otherwise known as vitamin H or coenzyme R, is present in many materials of both animal and vegetable origin, especially in beer wort, yeast, egg yolk, liver, tomatoes and carrots. It was first isolated from egg yolk and later from liver, and it was recently synthesized by Du Vigneaud and his associates from aliphatic compounds. It is a substituted fused ring composed of imidazoline and hydrothiophene.



TRIAZOLES AND TETRAZOLE

Metrazol N.N.R. (Leptazol, Cardiazol) is a white, odorless, crystalline powder that is readily soluble in water, alcohol or other solvents to give neutral solutions. It contains about 40.5 per cent of nitrogen and gives, with mercuric chloride, a white precipitate that can be identified by its melting point. It can be made by the reaction of hydrazoic acid on cyclohexanone in benzene solution; chemically, it is pentamethylene-tetrazole.



The action of metrazol is a rapid stimulation of the central nervous system, chiefly medullary and cerebral but also on the spinal cord. The effect is produced promptly after intravenous injection, usually within one minute, and the chief result is a series of clonic convulsions of comparatively short duration. This is used in the treatment of mental disorders, particularly in schizophrenia and depressive psychoses. The method is superior to that with camphor and safer than with insulin, but has largely been replaced by the simpler and safer electrical methods. It is contraindicated in the presence of cardiovascular or pulmonary disease and spinal injuries. The patient may be protected from fractures or dislocations of the extremities or spine by previous injections of curare. Metrazol is administered intravenously, intramuscularly or subcutaneously, using 0.1-0.3 gram, sometimes orally in the same amount several times daily.

Metrazol is an effective antidote for

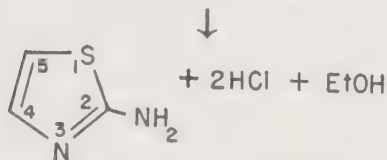
poisoning by depressant drugs, although it is probably inferior to picrotoxin and contraindicated in morphine poisoning. It is particularly used to counteract the effects of overdoses of the barbitals or of chloroform. It has also been recommended as a stimulant to the circulation in collapse or shock, but is probably without effect and may be harmful.

Triazol 156 (Azoman, Hexazole), 3-ethyl-4-cyclohexanyl-1,2,4-triazole, has been used in Europe as a substitute for metrazol in the treatment of mental disorders. It is claimed to be effective in smaller doses and decidedly less unpleasant for the patient, but it may have a deleterious effect on the bone marrow.¹¹ The dose recommended is 0.06 to 0.12 gram intravenously.

Another important derivative of triazole is Nitron, a reagent for detecting nitrates and picric acid; it is 1,4-diphenyl-3,5-endanilodihydro-1,2,4-triazole.

THIAZOLE

Thiazole is a colorless liquid boiling at 115-118° C. and very slightly soluble in water. It can be prepared from its 2-amino derivative by diazotizing in alcoholic solution, just as benzene can be made from aniline. The amine, which is commercially available, is prepared by heating α,β -dichloroethyl ether with thiourea.



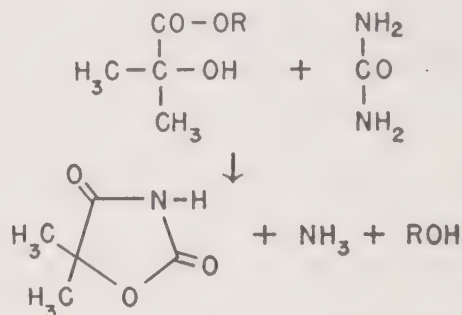
In chemical properties, thiazole is very much like benzene, but nitration and sulfonation are more difficult to perform.

Some of the important derivatives are sulfathiazole and related compounds, which are discussed elsewhere. For their preparation, 2-aminothiazole and its substitution products are necessary; the last may be made from aliphatic materials by methods that are analogous to that for the amine. Penicillin

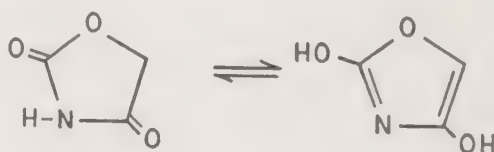
also belongs in this class and will be discussed among the antibiotics.

OXAZOLE

Synthesis of oxazole derivatives is accomplished by the reaction of urea and sodium ethylate on esters of α -hydroxy acids. Thus, trimethadione can be made from methylactic ester and methylation of the product.



They can be considered as from oxazole or its reduction forms, oxazoline and oxazolidine. Thus, 2,4-dihydroxyoxazole can tautomerize to 2,4-diketo-oxazolidine.



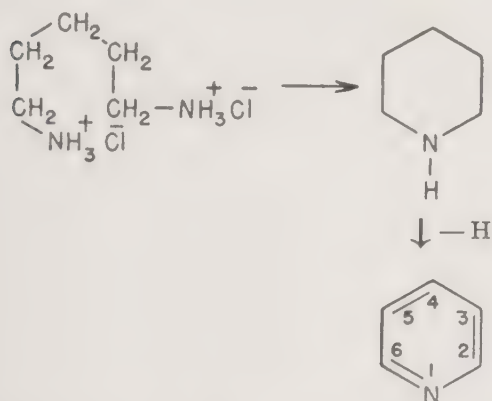
Trimethadione (Tridione) N.N.R., 3,5,5-trimethyl-2,4-diketo-oxazolidine, is a white, granular, crystalline substance with a slight, camphorlike odor. It is soluble in water or alcohol to give acidic solutions. It gives a white precipitate with barium hydroxide and is easily hydrolyzed by boiling alkalis. It possesses hypnotic, analgesic and anticonvulsant properties and is chiefly used in the petit mal seizures of epilepsy, particularly in the ideopathic forms; in the grand mal, it is of little value and may even be harmful. The dosage requires very careful supervision and must be determined individually for each patient, usually 1 to 2 grams daily or 3 to 7 capsules of 0.3 gram each, for children under six years 0.15-0.3 gram three times daily.

The most outstanding effects of toxicity are gastric irritation, nausea, skin eruptions,

photophobia, disturbances of vision, dizziness and drowsiness. Recently, there have been observed cases of aplastic anemia, which indicates the need for caution in administration and perhaps contraindicating the drug in anemias, leukopenia, thrombocytopenia or any type of blood dyscrasia. It should not be used in patients with advanced renal or hepatic disorders or with diseases of the optic nerve.

PYRIDINE AND PIPERIDINE

Pyridine was discovered in coal tar in 1846 and was later found in bone oil and in the products of pyrolysis from many organic materials. It can be made by the catalytic dehydrogenation of piperidine, which, in turn, is produced by heating salts of cadaverine, 1,5-diaminopentane.



Piperidine also can be obtained by the hydrolysis of piperine from pepper or by the reduction of pyridine with zinc and acetic acid.

Pyridine, a colorless liquid with a characteristic odor and a sharp taste, has a specific gravity of 0.99 and boils at 115-118° C. It is miscible with water and with most organic solvents and is itself an excellent solvent for many compounds. Although it is a very weak base, as might be expected because of the negative character of the resonant molecule, it forms fairly stable salts with strong acids. It has been used in medicine as an antiseptic and antispasmodic, but its efficiency for these purposes is considered low.

In chemical properties, pyridine and its substitution products are very similar to corresponding compounds of the aromatic series, but the nuclear hydrogen is more resistant to reagents. Chloro- and bromo- substitution can be accomplished with difficulty, as can also sulfonation using the fuming acid at higher temperatures. Nitro derivatives can be made, but nitric acid will not act directly with ease. After a group is introduced in place of hydrogen, it behaves very much in the same way as it does in aromatic compounds.

Some of the alkyl derivatives are found in pyrolytic materials of various kinds and can be oxidized to acids. The three monomethylpyridines, or picolines, are separated from coal tar in small amounts. α -Picoline boils at 130° C. and oxidizes to picolinic acid, α -pyridinecarboxylic acid; β -picoline boils at 143° C. and oxidizes to nicotinic acid, β -pyridinecarboxylic acid; γ -picoline boils at 144° C. and oxidizes to isonicotinic acid, γ -pyridinecarboxylic acid. Some of the six dimethylpyridines or lutidines are found in coal tar and in bone oil. Upon oxidation they furnish dicarboxylic acids, which may lose carbon dioxide and thus become changed to one of the mono acids noted above. The six trimethylpyridines or colidines are also known. The most important of the acids is nicotinic acid, which is one of the B vitamins and, together with its amide, will be considered later.

Piperidine is a colorless liquid with a pepperlike odor, boiling at 105-106° C., miscible with water and insoluble in alcohol. It is a strong base, $K=1.6 \times 10^{-3}$, and is easily attacked by the halogens, as are the cycloparaffins. Therefore, it is comparatively easy to introduce functional groups in place of the nuclear hydrogen, but the derivatives are often made by cyclization of aliphatic compounds.

Cetylpyridinium Chloride (Ceepryn Chloride) N.N.R. is a white, crystalline powder that is soluble in water or alcohol. It is a quaternary salt of the zephiran type

and is made by warming together pyridine and cetyl chloride. It is recommended as a surgical antiseptic and bactericide and is claimed to kill staphylococci in a concentration of 1:50,000 in ten minutes. It is subject to the same objections as other cationic detergents, chiefly that of being opposed by anionic types such as soap. It is furnished as a solution (1:1,000) and as colored or uncolored tinctures and has also been applied in the form of a vaginal powder or as vaginal suppositories (see Chapters 10 and 21).

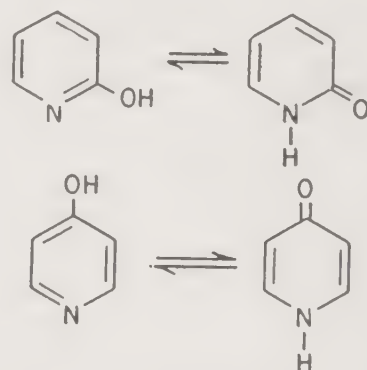
Quatresine (Tetradecyl- γ -picolinium chloride) is used in a similar manner.

Nikethamide N.N.R., the diethyl derivative of nicotinamide, $\text{Et}_2\text{N}-\text{CO}-\text{C}_5\text{H}_4\text{N}$, was introduced into medicine under the title of Coramine. It occurs as a colorless to pale yellow liquid with a somewhat viscous character, a slight aromatic odor and a peculiar, bitter taste. It is miscible with water, alcohol or ether, and the pH of the aqueous solution is about 6.2. It is easily hydrolyzed to nicotinic acid and is decarboxylated to pyridine by heating with alkalis.

The physiologic action of nikethamide is mainly one of stimulating the central nervous system. In animals this gives rise to increased rate and depth of the respiration and peripheral vasoconstriction, but in man the effects are variable and unreliable. As a respiratory stimulant in poisoning by morphine or chloral, it is perhaps useful, but it is inefficient for that caused by the barbitals. Because of its action on peripheral vascular tone, it may be of benefit in cases of acute

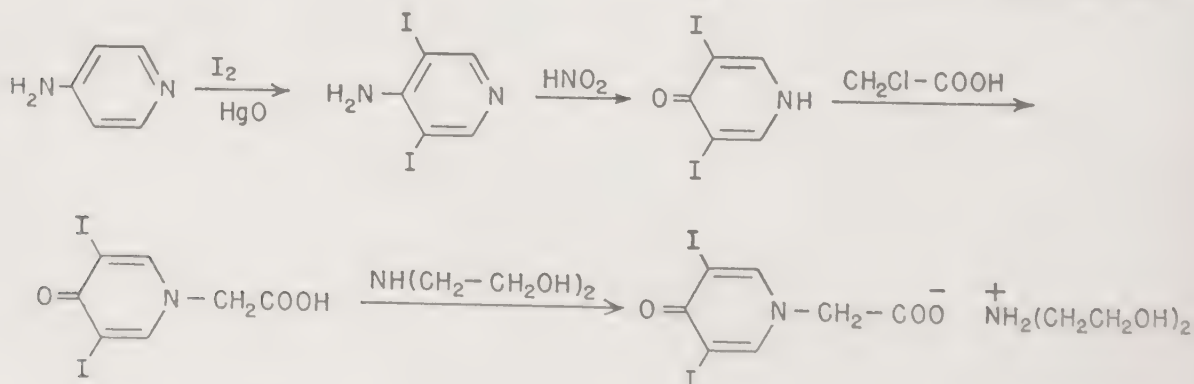
circulatory failure during surgical procedures or pneumonia, but it is contraindicated in the latter unless circulatory collapse supervenes. It is comparatively nontoxic since up to 30 cc. of the solution have been given without ill effect. It is administered intravenously in doses of 1 to 4 cc. of the available 25 per cent solution, but the rate must be slow with the larger doses because the drug is rapidly detoxified.

The alpha and gamma hydroxypyridines are called pyridones because they are tautomeric and probably exist chiefly in the ketonic forms.



A number of iodine derivatives of these are useful for roentgenography.

Iodopyracet Injection U.S.P. (Diodrast Solution) is a sterile solution of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and "contains, in each 100 cc., not less than 34 Gm. and not more than 36 Gm. of the salt." The separated acid "contains not less than 61.5 per cent and not more than 63.5 per cent of iodine (I)." It can be made in a number of ways, and the following outline is merely a typical one.¹²



The solution is used by intravenous injection of 10 to 30 cc. as a contrast medium in the roentgenographic visualization of accessible parts of the body, such as renal cavities, ureters, biliary tract, blood vessels, the heart and large vessels, etc. The patient is given a preliminary test to determine individual sensitivity by instillation into the conjunctival sac of a small amount, then a cathartic is given the night before the injection, and food and liquid are withheld for at least 18 hours previously to prevent blurring of the pictures. The solution is warmed to 98° C. and injected slowly into the vein and with careful observation of the patient. When renal functioning is normal, good exposures are obtained in from 5 to 15 minutes. For retrograde pyelography the solution is diluted with normal saline to about 15 per cent and allowed to flow by gravity through a catheter that has been inserted into the ureteral orifice by means of a cystoscope, about 20 cc. being required. For the visualization of the blood vessels or heart, a solution of special concentration (70 per cent) is used, and the technic is more complicated. In all of these methods, mildly toxic reactions are quite frequent, but serious ones are rarely encountered providing that the patient has been tested for susceptibility, that the injections are not repeated too often on the same individual and that contraindicating diseases are not present. The most serious ones are cyanosis and a fall in blood pressure, which lasts for less than an hour and can be overcome by epinephrine.

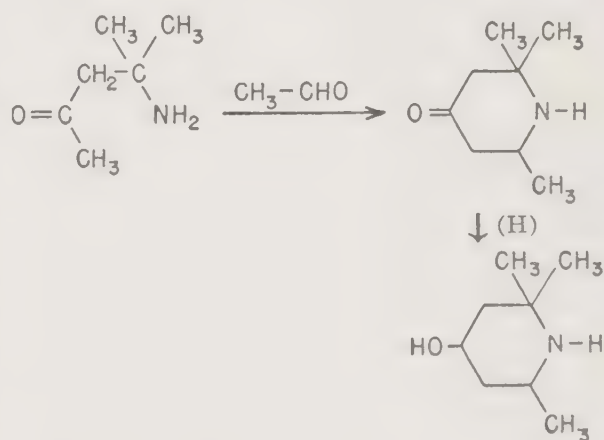
Iopax (Uroselectan), sodium 5-iodo-2-pyridone-N-acetate, is a yellow, pungent, crystalline powder that dissolves easily in water and contains about 43 per cent of iodine. It was designed for opaque-shadow photography to take the place of Selectan, 5-iodo-2-pyridone, but has itself been superseded by Neo-Iopax.

Neo-Iopax N.N.R. (Iodoxyl), disodium 3,5-diiodo-1-methyl-4-pyridone-2,6-dicarboxylate, consists of a white, odorless, crystalline powder that is very soluble in water

and contains about 52 per cent of iodine. It is used as a contrast medium in intravenous urography and retrograde pyelography, using the same technic and observing the same precautions as for iodopyracet, although it seems to give fewer reactions. The dose is 20 cc. of a solution containing 15 grams of the compound.

Rayopake, a similar agent, is a 50 per cent solution of the diethanolamine salt of 2,4-dioxo-3-iodo-6-methyltetrahydropyridine-N-acetic acid.

Eucaïne Hydrochloride (Betaeucaïne Hydrochloride) N.F., the salt of 2,2,6-trimethyl-4-benzoxypiperidine, is a white, odorless, crystalline powder that is stable in the air but is affected by light. It is soluble in water (1:30), alcohol (1:35) or chloroform. The alcohol of this ester, 4-hydroxy-2,2,6-trimethylpiperidine, is prepared from diacetoneamine by action of acetaldehyde and reducing the product.

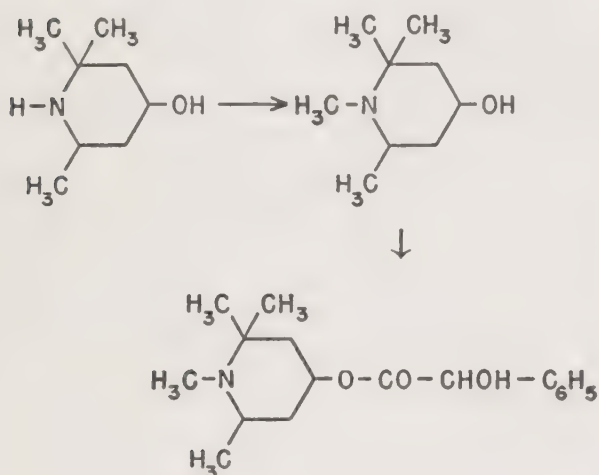


The ester then is made by benzoylation.

Eucaïne was introduced into medicine as a substitute for cocaine to produce local anesthesia. It has the advantages of not being vasoconstrictive, mydriatic or habit-forming, but it is also less efficient and more toxic than many newer compounds and is seldom used today. It is employed in 1 to 5 per cent solutions by injection, instillation or perfusion.

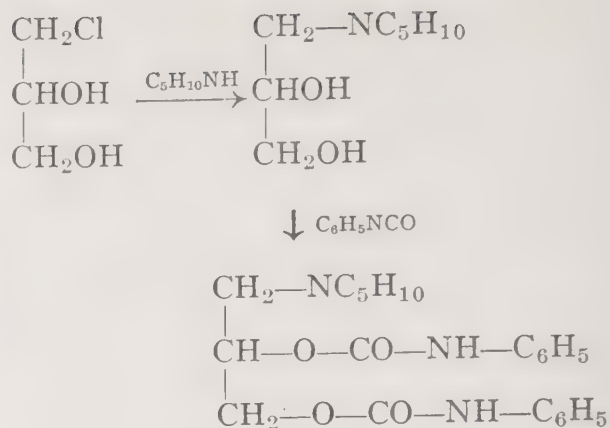
Eucatropine Hydrochloride U.S.P. (Euphthalmine Hydrochloride), the salt of 1,2,2,6-tetramethyl-4-mandeloxypiperidine, is a

white, granular, odorless powder that is very soluble in water or alcohol, and its aqueous solution is neutral to litmus. It is affected by light and should be preserved in light-resistant containers. With many of the alkaloidal reagents it gives precipitates, and it is particularly incompatible with solutions of basic substances. In its preparation the alcohol that was made for eucaine (q.v.) is first methylated and then esterified with mandelic acid.



Eucatropine is employed exclusively as a mydriatic for examination of the eye. It gives very prompt action without irritation of the cornea and produces very little interference with ocular tension or accommodation. The effects are of much shorter duration than they are with atropine or homatropine, and it is much less toxic and can be used when the patient is sensitive to either of them. Like other mydriatics, however, it may precipitate glaucoma in susceptible individuals. For mydriasis, 2-3 drops of a 5-10 per cent solution are instilled into the eye at 2 five-minute intervals; the effect wears off in about 2-3 hours.

Diperon Hydrochloride (Diothane Hydrochloride) N.N.R. is the hydrochloride of a base that is made by combining glycerol monochlorohydrin with piperidine in the presence of alkali and then adding phenyl isocyanate. It is a fine, white, odorless powder that is soluble in alcohol but not



much so in water; when applied to the tongue, it produces a bitter taste followed by a sense of numbness.

It is used as a local anesthetic in about the same way as cocaine and procaine, but it is claimed that the effects last much longer. After intravenous injection it is just about as toxic as cocaine, hence it should not be injected except in small amounts. It is recommended for the relief of pain and irritation in abrasions of the skin and mucous membranes, following hemorrhoidectomy, and in cases of non-operable hemorrhoids, and is applied in 0.5-1.0 per cent solution.

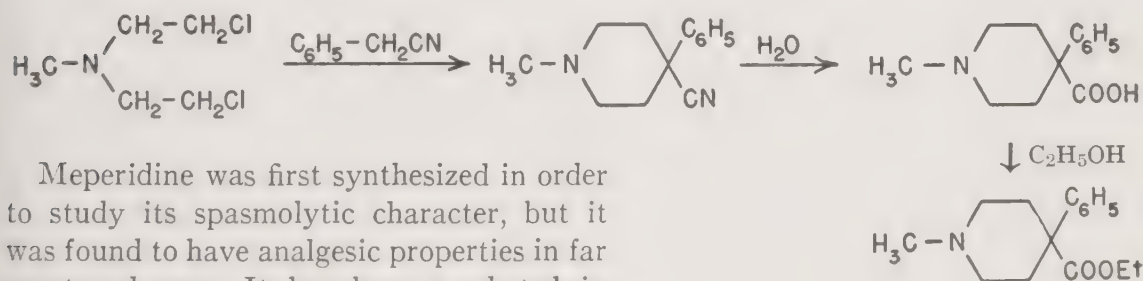
Piperocaine Hydrochloride (Metycaine Hydrochloride) N.N.R., the salt of 1-(3-benzoxypropyl)-2-methylpiperidine, is a fine, white, odorless, crystalline powder that is soluble in water or alcohol and on the tongue gives a slightly bitter taste followed by a sense of numbness. It contains an asymmetric carbon atom, but the racemic form is the one that is supplied.

Metycaine is used as a local anesthetic in much the same way as procaine; it has about the same toxicity subcutaneously but a much higher one intravenously. It is recommended for application to the eye in 2 to 4 per cent solutions, to the nose and throat in 2 to 10 per cent solutions, for infiltration in 0.5-1.0 per cent solutions, for nerve block in 1 to 2 per cent solutions and for spinal anesthesia in 1.5 per cent solutions with maximum quantity of the drug 1.65 milligrams per kilogram of weight. It is also

supplied in the form of ointments and tablets (see Chapter 15).

Surfacaine Hydrochloride, 3-(2-methyl-N-piperidinyl)propyl *p*-cyclohexyloxybenzoate hydrochloride, is a similar local anesthetic (see Chapter 15).

Meperidine Hydrochloride (Demerol Hydrochloride, Isonipecaïne) N.N.R. is the salt of ethyl-1-methyl-4-phenylpiperidine-4-carboxylate. It is a fine, white, odorless, crystalline powder that is soluble in water and only slightly so in alcohol. It is stable in the air at ordinary temperature, and its aqueous solution is not decomposed by a short period of boiling. The free base is made by heating benzyl cyanide with bis-(β -chloroethyl)methylamine, hydrolyzing to the corresponding acid and esterifying the latter with ethyl alcohol.¹³



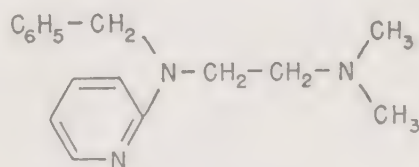
Meperidine was first synthesized in order to study its spasmolytic character, but it was found to have analgesic properties in far greater degree. It has been marketed in Europe under a variety of names, such as Dolantin, Dolantol, Pethidine, Eudolat, etc. The spasmolysis is due primarily to a direct papaverinelike depression of smooth muscle, but also to some action on parasympathetic endings. In therapeutic doses it exerts an analgesic effect which lies between that of morphine and codeine, but it gives little tendency toward hypnosis. It is indicated for the relief of pain in the majority of cases for which morphine and other alkaloids of opium generally are employed, but it is especially of value where the pain is due to spastic conditions of intestine, uterus, bladder, bronchi, etc. Its most important sphere seems to be in lessening the severity of labor pains in obstetrics and with barbitals to produce amnesia in labor. The dose is 0.05-0.15 gram intramuscularly or orally for routine analgesia. In labor, 0.1 gram is in-

jected intramuscularly as soon as contractions occur regularly, and a second dose may be given after 30 minutes if labor is rapid or if the cervix is thin and dilated (2-3 cm. or more). A third dose may be necessary an hour or two later, and at this stage a barbitol may be administered in small dose to insure adequate amnesia for several hours.

The question whether meperidine will cause addiction is not yet answered, although there seems to be psychic dependence in those individuals who experience a euphoria lasting for an hour or more. The development of tolerance has been observed, and it is significant that meperidine can be successfully substituted for morphine in addicts who are being treated by gradual withdrawal. Furthermore, mild withdrawal symptoms

have been noted in certain persons who have become purposely addicted to meperidine. The possibility of dependence is great enough so that it has been put under the Federal narcotics laws.

Tripelennamine Hydrochloride (Pyribenzamine Hydrochloride) N.N.R. the salt of N-benzyl-N'-dimethyl-N- α -pyridyl-ethylenediamine, is a stable, white, crystalline powder that is soluble in water to give a solution with a pH of about 6.6.



In guinea pigs it protects¹⁴ against 100 times the fatal dose of histamine (0.5-0.6

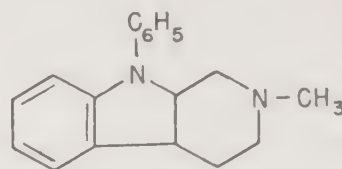
gram per kilogram) and answers the other criteria of antihistamine drugs (see histamine). Clinical experience has shown that it is as effective as diphenhydramine and may have the advantage of fewer and less intense side reactions, such as drowsiness, nausea, headache, dizziness, dryness of the mouth, nervousness and abdominal discomfort. It is absorbed well and is rapidly effective when given by mouth in a 0.05 gram dose several times daily, and this amount may be reduced to 0.025 gram in some cases or increased to 0.1 gram, or even 0.15 gram, if necessary. It is available in 0.05 gram tablets and in a 2 per cent ointment to relieve itching in atopic dermatitis, allergic eczema, pruritus ani, etc.

Neoantergan (Pyranisamine, Compound 2786 RP) is another of the drugs designed for use against histamine. It differs from pyribenzamine only by having a methoxy group in para position on the benzyl radical. It has been used extensively in Europe in doses about the same as pyribenzamine and in recent years has become popular in this country. It is claimed also to be a powerful local anesthetic and to have a quinidine-like action.

Methapyrilene Hydrochloride (Thenylene Hydrochloride) N.N.R., the salt of N-dimethyl-N'- α -pyridyl-N'-2-thenylethylenediamine, is also recommended as an antihistamine agent. It differs from pyribenzamine in having a 2-thenyl (thiophene-2-methylene) group in place of the benzyl. The drug is claimed to have marked action against histamine effects with considerably less incidence of side action. It is recommended in the treatment of all suspected allergies, especially for hay fever, allergic rhinitis, acute and chronic urticarias, allergic dermatitis and certain cases of asthma. The dose is 0.05 to 0.10 gram up to four times a day, and correspondingly less for children; it is supplied in tablets for this purpose.

Thephorin, another such agent, is the bitartrate of 2-methyl-9-phenyl-2,3,4,9-tetra-

hydro-1-pyridindene and, hence, has an entirely different structure.



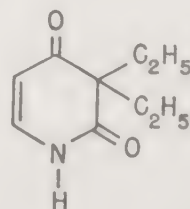
This is recommended in hay fever, allergic rhinitis, vasomotor rhinitis, bronchial asthma, atopic dermatitis, allergic eczema, angioneurotic edema, drug reactions (penicillin reactions, pruritus, barbitol dermatitis, sulfonamide reactions, joint-bone pains due to drug reactions), serum sickness and other allergic disorders. It is supplied in 25 milligram tablets and in a syrup containing 10 milligrams per 4 cc. The dose is 1 to 2 tablets up to three times a day or 2 to 4 teaspoonfuls of the syrup up to three times a day.

Diatrin Hydrochloride, N' dimethyl-N-phenyl-N-2(-thenyl)ethylenediamine monohydrochloride, is used like pyribenzamine.

Antistine, 2-(N-phenyl-N-benzylamino-methyl)imidazoline, is also recommended for use like pyribenzamine.

Mallophone (Pyridium), 2,6-diamino-3-phenylazopyridine hydrochloride, is a red powder that is sparingly soluble in water. It is claimed to inhibit the growth of staphylococci, streptococci, *E. coli* and gonococci and is recommended as a urinary antiseptic (1:200 to 1:100) or as antiseptic to the mouth, conjunctiva or urethra (1:1,000). The dose as urinary antiseptic is 0.2 gram three times a day.

Presidon (3,3-Diethyl-2,4-dioxotetrahydropyridine, NU-903) is a new sedative-hypnotic which is a pyridine derivative. The

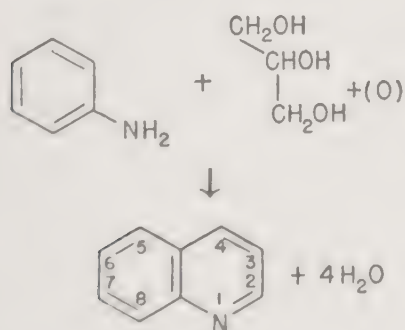


compound occurs in the form of colorless crystals, melting at 98°C .; it is soluble up to 2.5 per cent in water and readily soluble in alcohol, ether, chloroform, glycerin or olive oil. It is readily oxidized in alkaline media, resulting in a rupture of the pyridine ring at the double bond. Only about 6.6 per cent of the ingested drug is excreted in the urine. Perhaps the major part of Presidon undergoes oxidation in vivo.

Pharmacologically, the drug is a central nervous system depressant which produces motor paralysis, muscular relaxation and a deep sleep. In cases of mild and medium insomnia its quick onset and short duration are of distinct value. At present, only forms for oral administration are available.

QUINOLINE

Quinoline (Leucoline) occurs in coal tar, bone oil and other pyrolytic materials. It is a colorless liquid with a characteristic odor, a specific gravity of about 1.1 and a boiling point of $238\text{--}239^{\circ}\text{C}$. It is slightly soluble in water, but is miscible with alcohol and is soluble in strong acids to form fairly stable salts, in spite of the fact that its basicity is quite low. It can be prepared from quinine and other cinchona alkaloids but usually is manufactured by the Skraup synthesis, which is the oxidation of aniline and glycerol by means of arsenic pentoxide or nitrobenzene in the presence of sulfuric acid at high temperature.

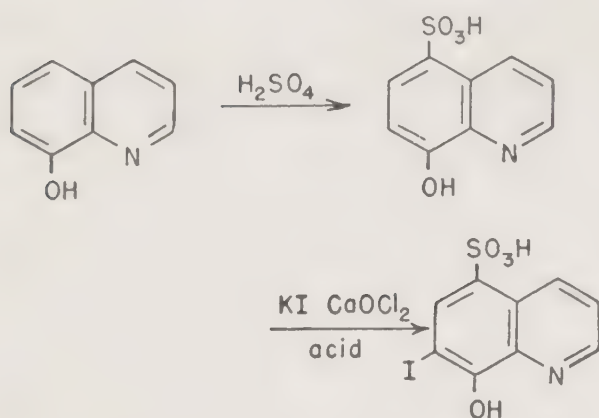


Almost any derivative that is desired can be obtained in an analogous manner, using substitution products of aniline and glycerol.

Quinoline has been used as an antiseptic for anatomic specimens and as an anti-malarial (the tartrate) in a dose of 0.3 to 1.3 grams, but its efficacy in either case is considered very low.

Oxine (8-Hydroxyquinoline, Quinophenol, Oxyquinoline) is a white, crystalline powder that is insoluble in water but soluble in alcohol, acids or bases. It is antiseptic if not actually bactericidal. The salts with acids are soluble in water and, therefore, more usable as antiseptics. Among others that have been employed are the citrate, tartrate (Termine), benzoate and sulfate (Chinosol, Quinosol). The last, which has been the most popular, is a yellow, crystalline powder that is fairly soluble in water to give an acid solution and has a bitter taste. It is presumably an active bactericide, having been given a phenol coefficient of 10 against *Staphylococcus aureus*, but its action against other organisms is variable and in most cases low. It is comparatively nontoxic, since it has been given to guinea pigs orally in doses as high as 3 grams without evident harm. As an antiseptic it is applied in concentrations of 1:3,000 to 1:1,000, and it has been administered orally in doses of 0.3 gram three times a day.

Chiniofon U.S.P. (Quinoxyl, Anayodin, Yatren) is a mixture of 8-hydroxy-7-iodoquinoline-5-sulfonic acid, its sodium salt and sodium carbonate, "containing not less than 26.5 per cent and not more than 29.0 per cent of Iodine (I)." It is a canary-yellow powder with a slight odor, a bitter taste, and a sweet after-taste. When added to water, it effervesces due to reaction with the sodium carbonate and finally dissolves (1:25). With ferric chloride in dilute solution it gives a deep, emerald-green color and with copper sulfate a dense, white precipitate. It is prepared by sulfonating 8-hydroxyquinoline, subjecting the product to potassium iodide and bleaching powder in the presence of potassium carbonate, precipitating the derived phenol with hydrochloric acid and finally mixing with sodium carbonate. (See next page for reaction.)



Chiniofon is used almost solely as a remedy in amebic dysentery, although it has also been employed like iodoform as a surgical dusting powder and in gonorrhea and diphtheria. The comparative advantages in amebic dysentery of chiniofon, vioform, diodoquin, carbarsone and emetine have not been determined, but most writers appear to think that the iodine compounds (first three) are safest and most effective and that chiniofon is the best choice in most cases. Toxic effects in therapeutic doses are seldom observed, except that many patients have a diarrhea during the first few days and that iodism may appear in the susceptible. The drug may be administered orally, using 0.25 to 1.0 gram (official dose 1 gram) three times a day for ten days or it can be given simultaneously in a retention enema of 3 grams in 100 cc. of water at not over $44^\circ C.$, in which case the oral dose is suspended or reduced during the rectal administration. In children the oral dose is 0.025 gram per kilogram three times daily.

Iodochlorohydroxyquinoline N.F. (Vioform), 5-chloro-8-hydroxy-7-iodoquinoline, "contains not less than 38 per cent and not more than 41.5 per cent of I, and not less than 11.4 per cent and not more than 12.2 per cent of Cl." It consists of a spongy, voluminous, brownish-yellow powder that has a slight, characteristic odor and is affected by light. It is practically insoluble in water or alcohol but dissolves in hot ethyl acetate and in hot acetic acid. It is decomposed by heating with dilute hydrochloric acid, more easily with concentrated sulfuric acid, giving

off vapors of iodine. It is prepared by iodinating 5-chloro-8-hydroxyquinoline, a direct product of a Skraup synthesis.

The compound originally was introduced as an odorless substitute for iodoform, for which it acts by slow liberation of iodine. It is used as an undiluted powder in surgery, in atopic dermatitis, in eczema of the external auditory canal, in chronic dermatitis, in oil dermatitis and in acute psoriasis and impetigo. It may also be applied as a 2-3 per cent ointment, emulsion or paste, or used in suppositories for the vagina in the treatment of trichomonas vaginitis.

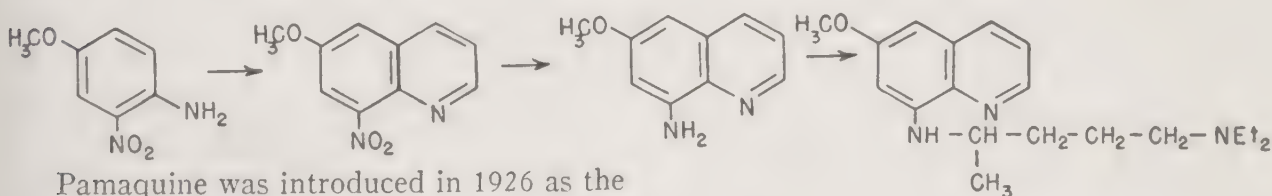
The chief use at present, however, is as a remedy in amebic dysentery. For this purpose it is more toxic than chiniofon but also more potent, and it can bring about apparent cures without any unpleasant symptoms, although in a few cases there may be abdominal distress, and the possibility of iodism is always present. The dosage is 0.025 gram three times daily after meals for 10 days, then a rest period of 7-10 days before the next series.

Diiodo-Hydroxyquinoline (Diodoquin, Yodoxin) N.N.R., 8-hydroxy-5,7-diiodoquinoline, is a yellowish-brown, odorless powder that is insoluble in water. It is recommended in the treatment of amebic dysentery and of infestation by *Trichomonas hominis (intestinalis)* and is claimed to be just as effective as chiniofon and much less toxic. However, several cases of acute dermatitis have followed its use. The dose is 7 to 10 tablets daily, each containing 0.21 gram, for 15-20 days; for children, the dose is one tablet for every kilogram of body weight three times daily.

Pamaquine Naphthoate (Aminoquin Naphthoate) N.F., the methylene bis- β -hydroxynaphthoate of 6-methoxy-8-(4-diethylamino-1-methylbutylamino)quinoline, "contains, when dried at 105° for 6 hours, not less than 43 per cent and not more than 45 per cent of 6-methoxy-8-(1-methyl-4-diethylamino)butylaminoquinoline (pamaquine base) and not less than 53 per cent and not more than 57 per cent of methylene-bis-

β -hydroxynaphthoic acid." It is a yellow to orange-yellow powder that is insoluble in water, soluble in alcohol or acetone; it is affected by light and gives a local anesthetic effect when placed on the tongue. With formaldehyde and sulfuric acid it gives a green color; hydrochloric acid precipitates from a solution in acetone a yellow substance, which, in water, gives a violet color with potassium iodate after about 2 minutes. Ether extracts from a suspension in sodium hydroxide T.S. a material that gives an intense blue color with chloranil in acetic acid.

Pamaquine base is made from 4-amino-3-nitroanisole, which is available from the dye industry. This is converted by the Skraup synthesis to 6-methoxy-8-nitroquinoline and then reduced to the amino compound. The latter is condensed with 4-bromo-1-diethylaminopentane, the same substance that is used in the final step in making quinacrine (q.v.).



Pamaquine was introduced in 1926 as the hydrochloride, under the title of Plasmochin or Praequine, to be used in malaria. In the avian form of malaria it is much more powerful than quinine and it seems to have a specific toxicity for the gametocytes of all forms of plasmodia. For this reason, it is especially of value in prophylaxis and in the treatment of infestation by *Plasmodium vivax*. It also is used particularly in selected cases, including carriers, where the gametocytes persist in the blood in spite of appropriate administration of other drugs. It also is employed with quinine, but not with quinacrine, in all forms of malaria. The dosage is 0.02 gram in the form of tablets or capsules several times daily for 3 to 5 days. Toxic reactions in about 10 per cent of the cases occur about 4 days after therapy has started. The symptoms are definitely alarming, and vigorous treatment must be started immediately when they appear. The chief

ones are jaundice, anemia, abdominal pain, nausea and vomiting, fever, weakness and urinary changes. The treatment consists of rest, high intake of carbohydrates and liquids, sodium bicarbonate and transfusions if necessary.

Pamaquine is used as the naphthoate because in this form it is less soluble and more slowly absorbed, thus allowing a more prolonged and uniform level in the blood.

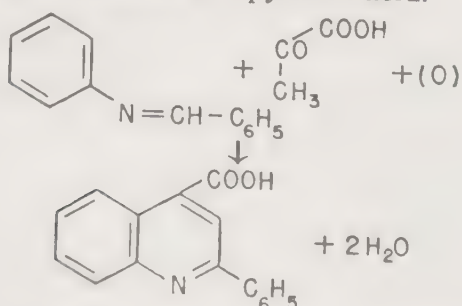
Pentaquine (SN 13,276) differs chemically from pamaquine in having the group $-(CH_2)_5-NH-CH(CH_3)_2$ in place of $-CH(CH_3)-(CH_2)_3-NEt_2$. It has been used for malaria as the diphosphate, which is in the form of yellow needles that are soluble in water and insoluble in alcohol and contain less than 5 per cent of impurities. It is rapidly and almost completely absorbed (80-90 per cent in 2 hours) and apparently decomposed in part, because only 15 per

cent appears in the urine. In 171 volunteers the toxicity was found to be one-half to three-fourths that of pamaquine, but the symptoms were qualitatively the same: anemia was encountered once, but no leukemia and only moderate leukocytosis. Pentaquine seems to be preferable to pamaquine in *P. vivax*. It is recommended in a daily dose of 0.4-0.8 gram (never more) with 2 grams of quinine in divided doses every 4 hours for 14 days. In the lower dose it seldom gives toxicity and is apparently quite effective.

Chloroquine Diphosphate (Aralen Diphosphate) N.N.R. (SN 7618), the salt of 7-chloro-4-(1-methyl-4-diethylaminobutyl)-quinoline, is a white, crystalline powder that is soluble in water but more soluble in very dilute acid. It is used in malaria in a manner similar to quinacrine. It is absorbed more readily and maintained at higher concentra-

tions when administered in the same amount, and is distributed according to the same pattern. Most of it is metabolized and only 10 to 20 per cent is excreted by the urine; after administration is stopped, the concentration falls about 60 per cent per week. The toxic reactions, which are about the same as with quinacrine, include headache, visual disturbances, pruritus and abdominal distress, but do not include discoloration of the skin. It is highly effective against erythrocytic forms of the plasmodium but does not prevent relapses in vivax malaria nor does it act as a prophylactic. It is most effective in suppressing attacks and lengthening the periods between attacks with much smaller doses than of quinacrine. The dose recommended is 0.3 gram each week, for acute symptoms 0.6 gram followed by 0.3 gram after 6 to 8 hours and again on each of two successive days.

Cinchophen (Phenylcinchoninic Acid, Phenylquinoline-carboxylic Acid) N.F., 2-phenylquinoline-4-carboxylic acid, was proposed in medicine many years ago as a remedy in gout, and has been marketed as Atophan, Atocin and Quinophan. It occurs as small, white or nearly white, needlelike crystals or as a fine, odorless powder that is stable in the air, is affected by light, has a slightly bitter taste and is practically insoluble in water. Its saturated solution in hydrochloric acid gives a yellow-brown precipitate with platinum chloride and it is easily decomposed by heat to phenylquinoline. Cinchophen may be prepared in several ways, of which one is condensation between benzylidenaniline and pyruvic acid.



Cinchophen causes a marked increase in elimination of uric acid, no matter what the

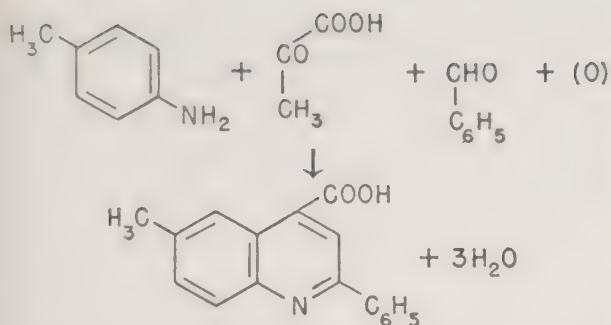
diet, by a mechanism that is unknown. Since increased uric acid in the blood is characteristic of the syndrome known as gout, it was thought that the drug should be of service in treatment of this disease and of other similar conditions. It does decrease the pain and help eliminate the uric deposits of gout and it also seems effective in relieving the pain of rheumatic fever and arthritis. The official dose of 0.5 gram usually is given three times daily suspended in plenty of water and preferably with sodium bicarbonate. Large doses often give all of the symptoms of cinchonism as observed with salicylates.

One of the chief objections to the use of cinchophen is the ever-present danger of causing serious liver damage in susceptible persons. This apparently has no relation to dosage and is difficult to counteract because it proceeds even if the drug is discontinued and sometimes even lasts for weeks after therapy has been terminated. The mortality, once the symptoms of liver damage have started, is nearly 50 per cent. The symptoms are nausea, vomiting, hepatic tenderness or pain and icterus, and these progress to death in coma 7 to 14 days after the beginning of the icterus; in nonfatal cases the recovery is slow. The smallest fatal dose that has been reported was 0.3 gram three times a day for six days.

The hydrochloride has been marketed as Chloroxyl and the hydriodide as Oxyl Iodide.

Neocinchophen, U.S.P. (Novatophen, Neoquinophan, Tolysin), ethyl 6-methyl-2-phenylquinoline-4-carboxylate, is a white to pale yellow, odorless, tasteless, crystalline powder. It is affected by light and is almost insoluble in water. Its alcoholic solution gives a yellow color with ferric chloride, while cinchophen gives a reddish-brown under the same conditions. It is prepared from benzaldehyde by heating under a reflux in absolute alcoholic solution with pyruvic acid and *p*-toluidine, subsequently esterifying with ethanol (see next page).

The therapeutic properties are very similar to those of cinchophen but it is appar-



ently less toxic and less liable to give fatal hepatic disease. Nevertheless, there have been a few deaths, and administration must be stopped at once if nausea, headache and abdominal distress are observed. Many physicians believe that the benefits to be derived in gout and similar conditions justify a risk of such toxic effects. The dose is 0.3 gram several times a day, preferably with sodium bicarbonate.

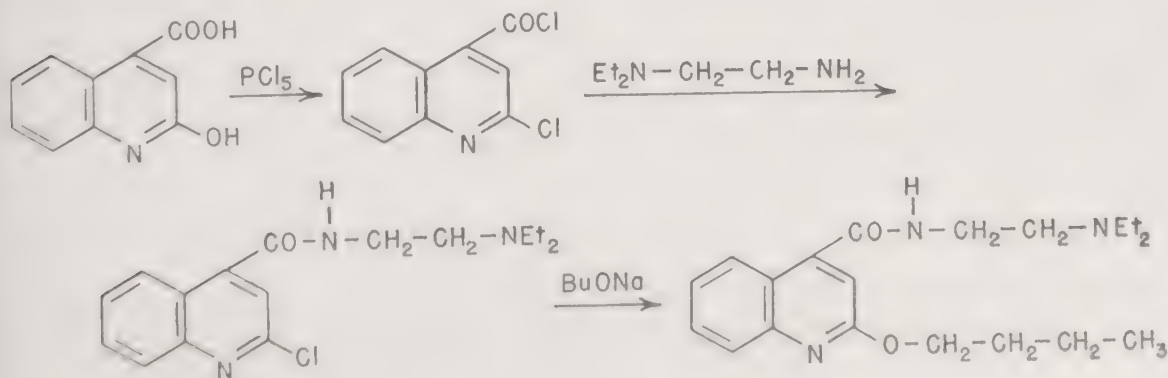
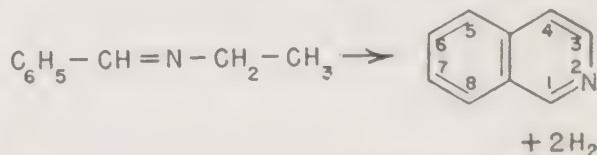
Other derivatives of phenylcinchoninic acid have been proposed, chiefly in Europe, with claims of lower toxicity that are not yet substantiated. The most popular of these was Atoquinol (Atochinol), the allyl ester, which occurs as odorless, yellowish crystals that are insoluble in water; it is given in doses of 0.05-1.0 gram. A combination of cinchophen (14 parts) and monoiodocinchophen (1 part) is sold in capsules under the name of Farastan. Others are Biloptin, 6-iodo-2-*p*-iodophenylquinoline-4-carboxylic acid; Isatophan, 8-methoxy-2-phenylquinoline-4-carboxylic acid, and Fantan, 2-phenylcinchoninyl urethane.

Dibucaine Hydrochloride (Nupercaine Hydrochloride) N.N.R. (Percaine), the salt of 2-butoxy-4-(β -diethylaminoethylcarbonyl)quinoline, is a white, hygroscopic,

crystalline powder that is freely soluble in water or alcohol. It is prepared from 2-hydroxycinchoninic acid by action of phosphorus pentachloride, condensation of the product with diethylethylenediamine and finally heating with sodium butylate.

Dibucaine is a powerful local anesthetic, being about 5 times as active as cocaine by injection and at least 20 times as strong when applied to the cornea, but it is also much more poisonous either subcutaneously or intravenously. It has been used considerably as a spinal anesthetic, for which it is injected in a concentration of 1:1,500 or less and never in amounts greater than 20 cc. (about 12 milligrams). For surface anesthesia and for injection it is employed in 1:2,000 to 1:1,000 solutions with the addition of 0.1 cc. of epinephrine hydrochloride solution (1:1,000) for every 100 cc. The solutions may be sterilized by autoclaving, but they are precipitated by even traces of alkali from glass and should be adjusted to pH 6.2 with acid.

Isoquinoline, found in coal tar in small amounts and probably also in other pyrolytic products, is a colorless liquid boiling at about 240°C . and insoluble in water. It or substitution products can be made by ring closure of aromatic compounds of the general type $\text{C}_6\text{H}_5-\text{C}-\text{N}-\text{C}-\text{C}$. For example, isoquinoline is prepared by distilling benzylidenethylamine through a red-hot tube.

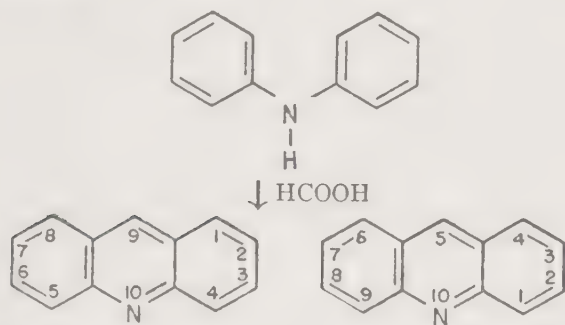


The nucleus of isoquinoline occurs in the structural formulas of several important alkaloids and other natural materials, notably papaverine, hydrastine and narcotine. Some synthetic compounds with this nucleus have been introduced into medicine, for example, eupaverine and perperine, which were designed as substitutes for papaverine.

Eupaverine, 3-methyl-5,6-methyleneoxy-8-(3,4-methyleneoxybenzyl)-isoquinoline, consists of colorless crystals. It is claimed to be stronger than papaverine in relaxing spasmodic conditions of smooth muscle and has been used for that purpose in doses of 0.03 to 0.06 gram.

Perperine, differing from papaverine by having four ethyl groups in place of methyl, is claimed to be more effective in the same doses and half as toxic. Both of these compounds are synthesized by methods similar to those used for the parent compound (q.v.).

Acridine may be regarded as derived from anthracene by replacing the carbon in position 9 with nitrogen. It occurs in coal tar and can be prepared by heating together diphenylamine, formic acid and zinc chloride.

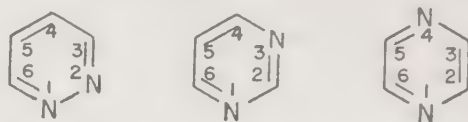


The numbering given first is that of Chemical Abstracts and usually is preferred in this country, but in England the second system is used. Acridine consists of colorless crystals that have a sharp odor, turn brown in the light, melt at 110° C. They are insoluble in water but dissolve in organic liquids and in acids to give a bluish fluorescence.

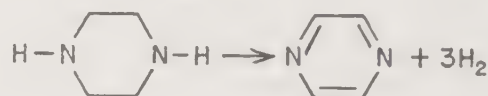
DIAZINES—PYRIMIDINE

There are three parent compounds that have a six-membered ring to include two nitrogen atoms, corresponding with the posi-

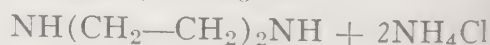
tions ortho, meta and para of the aromatic series. They are pyridazine, pyrimidine and pyrazine, respectively.



Pyridazine, a colorless liquid that boils at 204° C., furnishes a number of unimportant derivatives. Pyrimidine is a colorless solid that melts at 22° C., boils at 124° C., possesses a characteristic, penetrating odor and is soluble in water and the usual organic solvents. It furnishes a large number of important derivatives. Pyrazine is a colorless solid that melts at 55° C., boils at 116° C. and has an odor similar to that of heliotrope. It gives such important compounds as sulfa-pyrazine, safranine or phenazine dyes and riboflavin, all of which will be discussed in later chapters. Pyrazine itself may be prepared by distilling piperazine with zinc dust.



Piperazine (Arthriticin, Diethylenediamine, Dispermene, Hexahydropyrazine) occurs as colorless, volatile crystals that are freely soluble in water or glycerol. It crystallizes as a hexahydrate from water. It can be made by warming ethylene chloride with ammonia in alcoholic solution.



It was introduced into medicine because it will dissolve uric acid in a test tube, and it was hoped that this might be of service in gout and other rheumatic diseases. The clinical results, however, have been almost nil because the distribution of therapeutic doses could not be expected to furnish sufficient concentration. The claim that piperazine is a powerful diuretic has not been confirmed. The dose given is 0.3 to 0.6 gram several times daily.

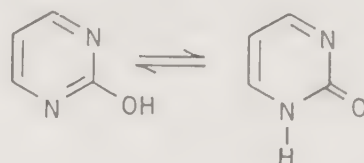
Lupetazine (Lycetal, Dimethylpiperazine) was at one time used for the same purposes but has no advantage.

Hetrazan, 1-diethylcarbamy-4-methylpiperazine, recently has been introduced for the treatment of filariasis.

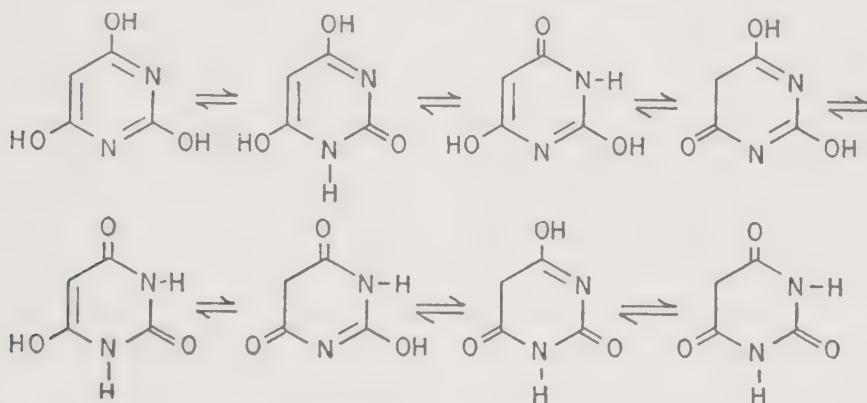
Pyrimidine, as has been noted, is by far the most important of the diazines because its nucleus is found in numerous natural products and in many manufactured drugs. Among those that will be discussed in later chapters are sulfadiazine, sulfapyrazine, thiamin, riboflavin and folic acid.

Nucleic acids are obtained from nucleoproteins, which are found in the nuclei of all vegetable and animal cells and also in the cytoplasm. These in turn hydrolyze to phosphoric acid, *d*-ribose or 2-desoxyribose, and

forms, probably in equilibrium. Thus, 2-hydroxypyrimidine is



With more than one hydroxy group on the carbon atoms, particularly in positions 2,4 or 6, there is the probability of a number of compounds in equilibrium. As an example, let us cite the formula 2,4,6-trihydroxypyrimidine (barbituric acid), which can undoubtedly exist in an equilibrium of eight different forms.



certain pyrimidine derivatives, which always include adenine, guanine, cytosine and either uracil or thymine. It will be noted that the pyrimidine nucleus contains the pattern of urea; hence, it is not surprising that the latter is the most important end product of protein metabolism, nor that other less degraded derivatives of pyrimidine, such as uric acid, are normal excretion products and also significant in pathology. The pattern of urea indicates further that synthetic compounds of this class can often be manufactured by starting with urea or its substitution products.

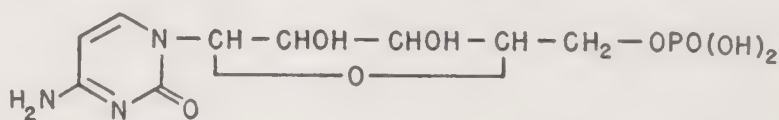
The hydroxy derivatives of compounds with the pattern of pyrimidine warrant special consideration. Since they contain the groups of $\text{C}=\text{COH}-$ or $-\text{N}=\text{COH}-$, they are enols and exist in other ketonic

The system, then, can behave as ketones or as enols at three positions, depending upon the reagents with which it is treated. The important result stems from the fact that the enolic forms are potential acids and might react with bases to form salts. In the compound cited only one of the enolic hydrogens (number 2) is easily replaceable, and barbituric acid is but a monobasic acid, while other similar substances such as uric acid are dibasic. The significant point is that one must visualize the tautomeric changes in order to understand chemical properties:

when $\text{C}=\text{COH}-$ or $-\text{N}=\text{COH}-$ is shown in a formula, one must also picture $\text{CH}-\text{CO}-$ or $-\text{NH}-\text{CO}-$ and vice versa.

Pentnucleotide is described as a mix-

ture of the sodium salts of nucleotides prepared from the nucleic acids of yeast by boiling with one per cent sodium hydroxide for 24 hours. The lead salts are made by precipitation and are decomposed by hydrogen sulfide, giving a solution of the acids which is concentrated and precipitated by alcohol. The sodium salts then are made by neutralization with sodium hydroxide. The final product, a clear, pale yellow solution, contains approximately 8 per cent of the sodium salts, has a pH of about 7.2 and is preserved with 0.3 per cent of cresol.



The important nucleoproteins of plants and animals can be deproteinized by a number of methods. Those of yeast are usually treated by grinding the materials with a very dilute solution of potassium hydroxide, adding picric acid in excess and precipitating the nucleic acids with hydrochloric acid. They are purified by dissolving in dilute potassium hydroxide, filtering, acidifying with acetic acid and finally precipitating with a large excess of ethanol.

The nucleic acids prepared in some such manner differ in a few respects according to source, but they seem to be remarkably alike in chemical composition. They are slightly soluble in cold water, more readily soluble in hot water and easily soluble in dilute alkalies, with the production of salt solutions, from which they can be precipitated by acids. Neutral solutions of the sodium salts from thymo-nucleic acids set to a jelly on cooling, but those from yeast do not. All of them can be hydrolyzed to nucleotides, and these in turn to nucleosides and finally to adenine, guanine, cytosine, uracil or thymine, ribose or deoxyribose and phosphoric acid. The first five are derivatives of pyrimidine, and the first two are purines, to be taken up later. The nucleotides

of yeast apparently are combined together in nucleic acids in a manner that is not well-understood, but the cementing units seem to be the ribose and phosphoric acid molecules. In any event, the nucleic acids are often spoken of as tetranucleotides because of the number of nucleotides arranged in the molecule.

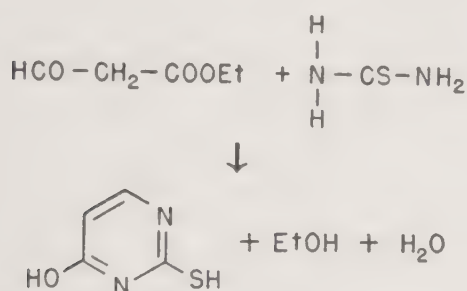
The nucleotides are made up of the pyrimidine derivative, the sugar (ribose or deoxyribose) and phosphoric acid. The arrangement of these, which has occupied the attention of many chemists for years, may be represented by the formula of cytidylic

acid, which furnishes cytosine, 6-amino-2-hydroxypyrimidine. Uridylic acid gives uracil, 2,6-dihydroxypyrimidine, and the third base, thymine, is 5-methyluracil or 2,6-dihydroxy-5-methylpyrimidine.

The nucleic acids of yeast, or their salts as represented in pentnucleotide, upon injection cause a marked temporary increase in leukocytes, preceded by a fall for from 6 to 8 hours. This suggested a value in aiding the blood to fight infectious conditions, but the results of trial did not confirm this. They also have been used in the treatment of rheumatic disorders on the basis of dissolving uric acid, and also in anemias because hematinics such as liver and bone marrow contain notable quantities of nucleic acids. The chief application, however, is in conditions accompanied by leukopenia or neutropenia, such as agranulocytosis caused by drug therapy (see aminopyrine). The dosage is 10 cc. of the 8 per cent solution injected into the gluteal muscle four times each day until clinical normalcy (temperature, count of leukocytes and polymorphonuclear neutrophils) is attained. If no response has been made after 10 days, further treatment with nucleic acids is probably useless. Toxic reactions of dyspnea, precordial distress or fever are infrequent, but in case they occur,

the effects may be minimized by administering the drug in divided doses into an anesthetized site.

Thiouracil, 6-hydroxy-2-mercaptopyrimidine, is a colorless, or slightly yellow, almost odorless, bitter, crystalline powder that is very little soluble in water or alcohol but soluble in alkalies; the aqueous solution has a pH of 4.8 to 5.5. It can be made by the condensation of thiourea with formylacetic ester, the latter by the Claissen reaction using ethyl formate and ethyl acetate in the presence of sodium methylate.



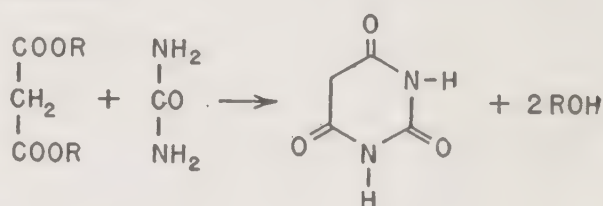
The compound interferes with the formation of thyroxine by the thyroid gland and, hence, reduces the symptoms of overactivity, as in hyperthyroidism. Since it does not inactivate or interfere with the hormone that is already formed, the effects of medication with thiouracil are not apparent until the store has been utilized in metabolism, which may require days or even weeks. Not all patients experience any permanent remission of symptoms, and because it is difficult to determine the necessary duration of treatment for this purpose, the drug is recommended only to prepare for an operative procedure or to reduce symptoms in those patients for whom operation is contraindicated. The initial dose is a 0.1 gram tablet four times per day until the symptoms are controlled and then 0.1-0.2 gram per day. In a high percentage of cases there are untoward reactions, the most frequent being agranulocytosis, leukopenia, fever and dermatitis, but jaundice, purpura, anemia and other symptoms have occurred. Patients should be warned to suspend medication at the least sign of any adverse effect, particularly sore

throat, fever, coryza or malaise. Thiouracil has also been recommended as a remedy in certain cardiac conditions, especially in congestive heart failure, auricular fibrillation and anginal syndrome.

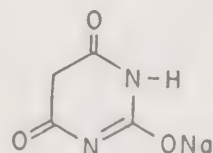
Propylthiouracil N.N.R., 6-propylthiouracil, has been found safer and more effective. It has a greater toxicity in equal amounts, but the dose required is considerably less and very few toxic reactions have been encountered. For example,¹⁵ in 54 patients treated with 0.025-0.05 gram per dose or 0.05-0.15 gram per day, a normal metabolic rate was established in four weeks. The ethyl and other alkyl derivatives have been used in the same manner.

BARBITALS

One of the important groups of pyrimidine derivatives is that of barbiturates or barbitals, the parent compound of which is barbituric acid or 2,4,6-trihydroxypyrimidine. This can be prepared by heating under pressure a mixture of malonic ester and urea in alcohol.



While theoretically it could act as a tribasic acid, actually only one hydroxyl, that in position 2, furnishes stable salts, such as sodium barbiturate, and the same is true of various substitution products.



By using derivatives of malonic ester or of urea or both, one can obtain almost an infinite variety of barbitals, all of which are monobasic acids. A great majority of the several hundred that have been made are 5,5-dialkyl derivatives and, therefore, are pro-

duced from dialkylmalonic ester. The enolic sodio-malonic ester reacts readily with alkyl halides to form the desired dialkyl malonic ester. Significantly, the monoalkylbarbituric acids are without physiologic effect. Some of the compounds also have —SH in place of —OH in position 2 (from thiourea), while still others have radicals on one or both of the nitrogen atoms and are made with substitution products of urea. Nearly 25 of them are used either as such or in the form of sodium or other salts.

All of the barbiturates are colorless, crystalline solids that melt at from 96°C. to 205°C. and are not very soluble in water, but form sodium salts that are quite soluble. Solutions of the latter are usually rather strongly alkaline and often hydrolyze enough to give precipitates of the barbital, and any admixture with acidic substances will be almost certain to give such a precipitate, an incompatibility that frequently must be considered in the dispensing laboratory. The alkalinity of the solutions can be largely overcome for parenteral injections by appropriate buffering.

Since the barbiturates are noted chiefly for their hypnotic action and are most important agents for this purpose, it will be well to consider here the mechanism by which this effect is produced. It is narcotic in the biologic sense in that it causes a reversible decrease or abolition of normal cell activities, but not in the legal sense in that it produces neither euphoria nor addiction with consequent withdrawal symptoms. The action of an ideal hypnotic would differ from that of a narcotic generally in that it would be exerted only on cells in the psychic center of the brain and on the centers of pain perception, with no effect on those of motor control, of the automatic process such as respiration and circulation or upon any other functions or glands. The ideal agent, therefore, would bring about sleep and freedom from pain without interfering with other normal processes, the effect should be of sufficient duration for the purpose intended and there should be no undesirable secondary reac-

tions. While no such agent has yet been discovered, the barbiturates appear to approach closest to these criteria, although chloral, paraldehyde, codeine and a few others seem to be of advantage under differing circumstances.

The mechanism by which hypnotics bring about the desired selective depression is not well understood. Indeed, no one knows just how narcotics in general affect the cell activities unselectively or why some of them act only on particular cells. The Meyer-Overton law, that the depressant efficiency of any agent is measured by lipoid solubility, is generally accepted as applying to hypnotics, but it is readily apparent from a knowledge of the physiologic action of thousands of compounds that other factors must also be considered, even for general narcotics. When it comes to explaining why such diverse chemical structures as barbital, chloral hydrate and sulfonal have a more or less selective action on the psychic center, a satisfactory theory is not forthcoming. It is known, for example, that barbital in vitro depress carbohydrate metabolism of the brain, probably through an interference with oxidation-reduction reactions of flavoprotein by the cytochrome system, but this does not explain in detail particular action on the psychic center.

Variations of action after administration of the barbiturates are not great, although those from particular ones may differ from the usual ones in certain respects. These variations from a practical standpoint involve chiefly dosage, how long after administration before the effects are observed, duration of action, ratio of therapeutic to toxic or fatal dose and extent of accumulation. Since the dosage can be regulated and the margin of safety is usually satisfactory, the main considerations are promptness and duration of action, chiefly the latter. The relation between structure and effect seems rather complex since other factors still unknown must probably be taken into account. Tatum,¹⁶ in 1939, made the following summary: (1) both hydrogens in position 5 must be re-

placed, (2) increasing the length of the substituting radical enhances the potency up to 5 or 6 carbon atoms, (3) branched chains give compounds with briefer action, (4) unsaturated radicals give briefer effects than saturated ones, (5) those compounds with alkyl groups in 1 or 3 have shorter action and may have stimulating properties, (6) replacement of oxygen by sulfur in 2 increases instability and shortens the action. It may also be said that a phenyl group makes the action greater and that a benzyl radical confers convulsant properties.

The effects following administration of the barbiturates pursue about the same course, no matter which of the compounds is used. Therapeutic doses in the smaller amounts calm nervous conditions of any origin and in larger amounts cause a dreamless sleep in from 20 to 60 minutes after oral administration and almost immediately if given intravenously. In some patients there may be considerable excitement before sedation is initiated. Still larger doses produce a form of anesthesia, and in all cases, up to this stage there is little disturbance of other functions, such as respiration, circulation, metabolism or the action of smooth muscle. The effects last for one-half to eight hours, depending on the compound, the dosage and the stage to which the narcosis has been carried, and the patient awakens refreshed, but may not be as alert as usual and may experience some lassitude for a time. In the presence of pain these drugs have very little analgetic action but may potentiate other compounds that do have such effect. Excretion is practically entirely by the kidneys, where they appear partly unchanged, partly more or less decomposed and partly conjugated. Some of the compounds, especially those containing sulfur, are almost entirely destroyed in the body, probably in the liver.

Untoward reactions are uncommon except with very large doses. The chief one of inconvenience is the appearance in some individuals of delayed effects, extreme depression, excitement or even mania. These clear up eventually and can often be prevented by

using a different barbitol. Occasionally, some persons are hypersensitive and experience dermatologic lesions as manifested by wheals, angioneurotic edema or scarletinal rashes. The respiration and circulation are depressed slightly by anesthetic doses, but the temperature and basal metabolism are scarcely affected. Relatively large amounts, however, as seen frequently in suicidal cases, cause profound and prolonged coma, a marked fall in blood pressure and eventual paralysis of the respiratory center. About 10 per cent of such instances result in death, but recovery often follows from very large quantities after adequate treatment and four to six days of coma. The remedial measures used are persistent administration of picrotoxin or similar agents, various supportive procedures and artificial respiration or oxygen if necessary. Even in therapeutic doses, there is an occasional fatal collapse due to peripheral paralysis of the blood vessels. The margin between therapeutic and toxic doses is comparatively large, and poisoning would be of little importance were it not for the fact that the barbiturates are easily obtainable and lead to accidental or deliberate overdosage. More than half of the states have already enacted laws designed to make them more difficult to obtain.

The question of whether the barbiturates can cause addiction as is observed with morphine or cocaine must be answered in the negative. It is true that millions of individuals are taking them to produce sleep and that many of them have the habit of doing so regularly. On the other hand, there is no appreciable change in the toxic dose after long continued administration, no euphoria upon initiation and no serious withdrawal symptoms. Therefore, the habit is not addiction in the usual sense, even if it is sincerely to be condemned. There should be laws to control purchase of the barbiturates.

The barbiturates are used chiefly as sedatives and hypnotics in a wide variety of conditions. Any of them will suffice for these

purposes, but naturally the most useful generally are those whose action lasts longest. The diseases for which sedation by them is indicated vary from a state of "overwrought nerves" to a violent mania; they have the advantage over the bromides that the action may be pushed to more profound states by increasing the dose, particularly to induce sleep. They are indicated in any type of insomnia that is not due to pain and, even in cases where pain is present, may advantageously be combined with analgetics. They are also applied to suppress all kinds of convulsions that originate in the central nervous system, including those from traumatic tetanus, meningitis, chorea, epilepsy, eclampsia, insulin overdosage and poisoning by strychnine and similar drugs. In epilepsy, phenobarbital or a similar barbiturate will diminish the number and severity of the attacks, although this lasts only during the medication, and combined treatment with hydantoin derivatives appears to be of advantage.

They also are employed to conduct anesthesia, either as premedication before other agents, to take a share in the process itself or to act as the sole anesthetic. In any preliminary sedation they are superior in some respects to morphine, and it often may be of advantage to combine the two. In somewhat larger doses they can assume a share in the narcosis, thus diminishing the amount of volatile anesthetic required and reducing the undesirable side effects of the latter. In obstetrics, amnesia can be brought about, the patient falls asleep between pains and does not remember them, and for this purpose, they may be combined with morphine or scopolamine. The production of surgical anesthesia by barbiturates for short operations is not without dangers, chiefly because of individual susceptibility, and it is naturally confined to those with very short action, such as thiopental or hexobarbital.

Barbital (Diethylbarbituric Acid, Barbitone, Diethylmalonylurea) U.S.P. (Veronal) is 5,5-diethylbarbituric acid. The official dose is 0.3 gram.

OFFICIAL OCCURRENCE	PER CENT BARBITAL
N.F.	
Barbital Elixir	3.5

Barbital Sodium (Soluble Barbital, Soluble Barbitone) U.S.P. (Medinal). The official dose is 0.3 gram.

Phenobarbital (Phenylethylmalonylurea, Phenobarbitone) U.S.P. (Luminal, Gardenal) is 5-ethyl-5-phenylbarbituric acid. The official dose is 0.03 gram.

OFFICIAL OCCURRENCE	PER CENT PHENOBARBITAL
U.S.P.	
Phenobarbital Elixir	0.4

Phenobarbital Sodium (Soluble Phenobarbital, Soluble Phenobarbitone) U.S.P. (Luminal Sodium). The official dose is 0.03 gram.

Pentobarbital Sodium (Soluble Pentobarbital) U.S.P. (Nembutal) is the sodium salt of 5-ethyl-5-(1-methylbutyl)barbituric acid. The official dose is 0.1 gram.

OFFICIAL OCCURRENCE	PER CENT PHENOBARBITAL SODIUM
U.S.P.	
Pentobarbital Sodium Capsules	...
N.F.	
Pentobarbital Sodium Elixir	0.4

Thiopental Sodium (Thiopentone Soluble) U.S.P. (Pentothal Sodium) is the sodium salt of 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid. The official dose for anesthesia is to be determined by the physician, but it usually is 2-3 cc. of 5 per cent solution initially.

OFFICIAL OCCURRENCE
U.S.P.
Sterile Thiopental Sodium

Allyl Barbituric Acid (Sandoptal) N.N.R. is 5-allyl-5-isobutylbarbituric acid. The dose is 0.2-0.8 gram orally as sedative and hypnotic. It is available in tablets containing 0.2 gram.

Amobarbital (Amytal) N.N.R. is 5-ethyl-5-isoamylbarbituric acid. The doses are as follows: 0.02-0.3 gram as a sedative and hypnotic, 0.2-0.6 gram as a pre-anesthetic and 0.4-0.8 gram as an anticonvulsant. It is

available in tablets of 0.008-0.096 gram and in an elixir containing 0.88 gram per 100 cc.

Amobarbital Sodium (Amytal Sodium) N.N.R. The dose is 0.2 gram as a sedative and hypnotic, repeated if necessary at 6-hour intervals; 0.4-0.8 gram orally or rectally as an anticonvulsant and 0.2-0.6 gram orally or rectally as a pre-anesthetic.

Aprobarbital (Alurate) N.N.R. (Numal) is 5-allyl-5-isopropylbarbituric acid. The dose is 0.065-0.13 gram orally as a sedative and hypnotic. It is available as tablets containing 0.065 gram and an elixir containing 0.9 gram per 100 cc.

Aprobarbital Sodium (Alurate Sodium) N.N.R. The dose is 0.01 gram per kilogram as a pre-anesthetic by oral or rectal administration. It is available as capsules containing 0.227 gram equivalent to 0.2 gram of aprobarbital.

Butabarbital Sodium (Butisol Sodium) N.N.R. is the salt of 5-ethyl-5-sec.butylbarbituric acid. The dose is 0.015-0.12 gram orally as a sedative and hypnotic and in obstetrics.

Butallylonal (Pernoston) N.N.R. is 5- β -bromoallyl-5-sec.butylbarbituric acid. The dose is 0.194 gram as a hypnotic. It is available in tablets containing 0.194 gram.

Butallylonal Sodium (Pernoston Sodium) N.N.R. The dose is 1 cc. of 10 per cent solution per 12.5 kilograms intravenously or intramuscularly as a hypnotic. It is available in ampules containing 2 cc. of 10 per cent solution.

Butethal (Neonal) N.N.R. (Soneryl) is 5-butyl-5-ethylbarbituric acid. The dose is 0.05-0.4 gram orally as a sedative and hypnotic. It is available as tablets containing 0.1 gram.

Cyclobarbital (Phanodorn) N.N.R. is 5-cyclo-1-hexenyl-5-ethylbarbituric acid. The dose is 0.1-0.4 gram orally as a sedative and hypnotic. It is available in tablets containing 0.2 gram.

Cyclopal is the sodium salt of 5-allyl-5-cyclo-1-pentenylbarbituric acid. The dose is 0.05-0.15 gram orally as a pre-anesthetic or in obstetrics.

Diallyl Barbituric Acid (Dial) N.N.R. is 5,5-diallylbarbituric acid. The dose is 0.03 gram as a sedative 3-4 times daily or 0.1-0.3 gram as a hypnotic. It is available as tablets containing 0.03-0.1 gram as a sterile solution with urethane containing 0.1 gram and as an elixir containing 0.0125 gram per cc.

Eunarcon is the sodium salt of 5- β -bromoallyl-5-isopropyl-3-methylbarbituric acid. The dose is 5-10 cc. of a 10 per cent solution intravenously as anesthetic.

Hexethal Sodium (Ortal Sodium) N.N.R. is the sodium salt of 5-ethyl-5-hexylbarbituric acid. The dose is 0.2-0.4 gram orally or rectally. It is available in capsules containing 0.05, 0.2 and 0.3 gram.

Hexobarbital (Evipal, Hexobarbitone, Evipan, Cyclural) is 5-cyclo-1-hexenyl-3,5-dimethylbarbituric acid. The dose is 0.25-0.5 gram as a hypnotic.

Hexobarbital Soluble (Evipal Sodium, Evipal Soluble) N.N.R. (Sodium Hexobarbitone, Cyclural Sodium). The dose is 2-4 cc. of a 10 per cent solution intravenously for anesthesia, with an additional 1-2 cc. if necessary; a total of more than 10 cc. is dangerous. It is available in ampules containing 0.05 and 1 gram of the salt.

Kemithal is 5-allyl-5-cyclo-2-hexenyl-2-thiobarbituric acid. The dose is 0.5-6.3 grams of sodium salt intravenously for anesthesia in the form of a 5 to 10 per cent solution.

Mebaral (Mephobarbital, Prominal, Phemitone) is 5-ethyl-3-methyl-5-phenylbarbituric acid. The dose is 0.03-0.4 gram in epilepsy 1 to 3 times daily.

Probarbital Calcium (Ipral Calcium) N.N.R. is the salt of 5-ethyl-5-isopropylbarbituric acid. The dose is 0.12-0.25 gram orally as a sedative and hypnotic. It is available in tablets containing 0.05 and 0.13 gram.

Probarbital Sodium (Ipral Sodium) N.N.R. The dose is the same as that of the calcium salt. It is available in tablets containing 0.25 gram and in an elixir containing 0.013 gram per cc.

Propallylonal (Nostal, Noctal) is 5- β -bromoallyl-5-isopropylbarbituric acid. The dose is 0.05-0.3 gram orally as a sedative and

hypnotic. It is available as tablets containing 0.1 gram.

Seconal Sodium N.N.R. is the salt of 5-allyl-5-(1-methylbutyl)barbituric acid. The doses are 0.1-0.2 gram orally or rectally as a sedative and hypnotic, 0.3 gram initially and up to a total of not over 1.2 gram orally or rectally in obstetrics and 0.2-0.3 gram orally as a pre-anesthetic. It is available in pulvules of 0.05 and 0.1 gram, in ampules containing 0.25 and 0.5 gram of the salt, in suppositories containing 0.13 and 0.2 gram and in an elixir containing 0.44 gram per 100 cc.

Sigmodal Sodium is the salt of 5-sec.amyl-5- β -bromoallylbarbituric acid. The dose is 10 cc. of a 10 per cent solution rectally in obstetrics.

Vinbarbital Sodium (Delvinal Sodium) N.N.R. is the salt of 5-ethyl-5-(1-methyl-1-butenyl)barbituric acid. The doses are 0.032 gram orally 3 to 4 times daily as a sedative, 0.1-0.4 gram as a hypnotic and 0.2-0.4 gram in obstetrics. It is available in capsules containing 0.03, 0.1 and 0.3 gram and as an elixir containing 0.26 gram in 30 cc.

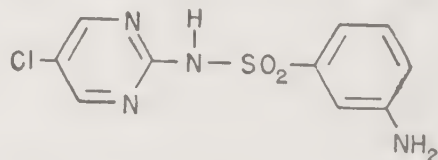
As has been noted, the choice of agent in each case rests almost entirely upon the duration of action. Any of those that give moderate or long-continued action, and this includes the majority of the ones listed, could be employed as sedative or hypnotic, but the most popular as sedatives are phenobarbital and barbital, as a hypnotic, pentobarbital. In epilepsy, where powerful and sustained action is necessary, phenobarbital and mebaral are the agents of choice, but amobarbital and others have been used in this way. As preparation for anesthesia and in obstetrics, those compounds with moderate or short duration are desirable, and those recommended are seconal, amobarbital, vinbarbital, sigmodal, aprobarbital, cyclopal and butabarbital. As anesthetics or to assist in anesthesia, thiopental is preferred because of its short action, but included also are eunarcon, hexobarbital and kemithal. It will be observed that all of these have a radical

on the nitrogen or have sulfur in place of oxygen.

Other simple derivatives of barbituric acid are of lesser importance, but some of them are useful as reagents and in synthesis. The hydrogen atoms in position 5 are easily attacked by reagents. Violuric acid, 5-isonitrosobarbituric acid, is obtained by the action of nitrous acid, and this can be oxidized to give the nitro compound, dilituric acid, or reduced to the amino derivative, uramil. Oxidation of the parent compound results in replacing the two hydrogens by oxygen to give alloxan, while halogenation easily can be brought about to introduce two halogen atoms.

Dibromin, 5,5-dibromobarbituric acid, is a colorless, crystalline solid containing about 56 per cent of bromine. It is soluble in water (1:33) to give a solution that decomposes rapidly to hypobromous acid and bromine. It is claimed to be much more bactericidal than phenol and to be nontoxic and not irritating. It has been recommended as surgical disinfectant, using 1:10,000 to 1:1,000 concentrations.

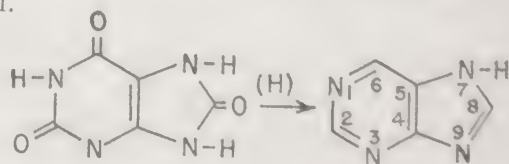
Metachloridine, 2-(*m*-aminobenzenesulfonamido)-5-chloropyrimidine, has been



proposed in malaria. It is a sulfa drug and is made by the action of 5-chloro-2-aminopyrimidine on *m*-sulfanilyl chloride.

PURINE

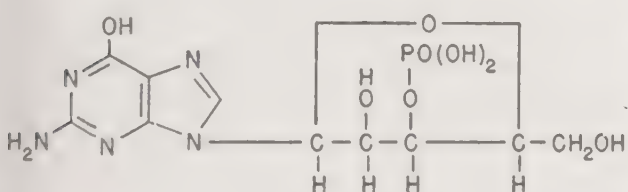
Although this compound is of no practical importance itself, it is the parent of several natural substances that have great significance in biology and medicine. It can be made from them in a number of ways, best illustrated by the indirect reduction of uric acid.



From the formulas it will be observed that uric acid is 2,6,8-trihydroxypurine and that purine is composed of pyrimidine and imidazole rings fused together at 4,5 positions in each. It also will be noted that the positions 1,2,3 and 7,8,9 are of the urea pattern.

As will be remembered, two of the compounds from nucleic acids of any origin are adenine, which is 6-aminopurine, and guanine, which is 2-amino-6-hydroxypurine. When the nucleoproteins are split to remove the protein, nucleic acids or nucleins are produced, and these in turn can be hydrolyzed to several (usually four) nucleotides, those of adenine, guanine, cytosine and either uracil or thymine. The nucleotides are bound together in some unknown manner through the ribose and phosphoric acid. Upon further hydrolysis they are decomposed to nucleosides and phosphoric acid, and still further action gives the pyrimidine derivative and *d*-ribose or deoxyribose. In the case of adenine and guanine, the sugar molecule is probably combined to nitrogen in position 9.

Guanylic acid, which is found free in the liver, the spleen and the pancreas, and in yeast, can be produced from nucleic acids. It has the probable formula



It hydrolyzes to the nucleoside guanosine, which in turn gives ribose and guanine. Furthermore, it is deaminated in the body by the enzyme guanase to xanthylic acid, which can be split to phosphoric acid and xanthosine, the latter further to ribose and xanthine, 2,6-dihydroxypurine.

Adenylic acid, as obtained from nucleic acids, probably has a similar structure, but another form of it, which is an important ingredient of muscle and concerned with carbohydrate metabolism, has the phosphoric

acid on the fifth carbon atom of ribose. It hydrolyzes to phosphoric acid and the nucleoside adenosine, which in turn gives adenine and ribose. It is also deaminated in the body by adenase to inosinic acid (carnine), which can be split to phosphoric acid and inosine, the latter further to ribose and hypoxanthine, 6-hydroxypurine. This and xanthine are important as products of metabolism, but xanthine is also the parent of caffeine and its associated compounds, which are methyl derivatives. Furthermore, it can be oxidized to uric acid which is so significant in the physiologic processing of purines.

Adenine, 6-aminopurine, occurs as white needles that are slightly soluble in water or alcohol. It and its combination with ribose and phosphoric acid are said to influence diuresis, muscular activity and the central nervous system much as do the xanthine derivatives. The sulfate has been used by intravenous injection in the treatment of agranulocytosis, the dose being 1 to 2 grams in 30 to 60 cc. of isotonic salt solution.

Caffeine U.S.P. (Theine, Guaranine), 1,3,7-trimethylxanthine or 2,6-dihydroxy-1,3,7-trimethylpurine, occurs as a white, odorless powder or as white, glistening needles that have a bitter taste. It "contains not more than 8 per cent of water of hydration." It is somewhat soluble in water (1:50) and in alcohol (1:75), and its aqueous solution is neutral. With tannic acid it gives a precipitate that is soluble in excess; with iodine and hydrochloric acid it gives a red-brown precipitate that dissolves in sodium hydroxide solution. It gives a positive murexide test like other derivatives of purine. This is performed by evaporation to dryness with hydrochloric acid and potassium chlorate and exposure of the residue to vapors of ammonia, giving a deep purple color of murexide that is destroyed by alkalis.

Caffeine occurs in many plants, can be made from other natural compounds in several ways or may be synthesized com-

pletely. It is extracted from tea (about 3 per cent), from coffee (about 1.2 per cent), from guarana (4 per cent) and from Kola (about 1 per cent), but is chiefly obtained from warehouse wastes of tea and the decaffeination of coffee. From theobromine or theophylline it can be prepared by methylation and from uric acid by reduction and methylation, or it may be synthesized completely, as is also uric acid. Future supplies may need to be furnished partly in the last way, because the demand (mostly for commercial beverages) is steadily increasing, now more than 500 tons annually in the United States.

In pharmacy, various combinations are employed to increase solubility and effectiveness. It is a very weak base so that its salts are too easily hydrolyzed to be stable and, hence, not available for administration. However, it is much more soluble in solutions of other salts and acids, such as sodium salicylate, sodium benzoate, and citric acid, and such combinations are suitable for injection.

In physiologic action, caffeine and its relatives theobromine and theophylline are qualitatively alike. The primary effect from therapeutic doses is a stimulation of the central nervous system, beginning in the psychic center and progressing downward, with little or no reversal by continued or larger doses. There is also a direct stimulation of all muscles, partly central and partly peripheral, an increase in diuresis, and vasodilation by direct action on particular vessels. The dominant effect on the psychic center causes increased flow of thought, lessens drowsiness and mental fatigue, relieves headache and gives a sense of comfort and well-being. In combination with the action on muscles, it brings about a condition in which more work can be done before fatigue sets in, and this is performed more rapidly and accurately, although later there may be impairment of these qualities for some time. The breathing is only moderately stimulated but more intensely if already in a depressed state. The effects on the circula-

tion are somewhat complex because of the conflicting central and peripheral actions. The vagus is incited, giving a tendency to slow the pulse, but the muscular tissue is affected in the opposite way, generally to predominate. With very small doses, the pulse may be slower and stronger than normally, an effect that would theoretically be comparable to that from digitalis, if the diastolic relaxation were not absent. The large action on the vasomotor center tends to raise the blood pressure, which is also favored by heightened pulse, but this is counteracted by effect on the muscles of the vessels. The total circulatory change may be assumed to be little or nothing under ordinary conditions, but in cases of poisoning there may be faster pulse and increase in blood pressure.

The diuresis, which is rather pronounced, is apparently even more complicated and not well-understood. For years it was assumed that this was due to direct action on the renal epithelium, but more recent experiments indicate explanations in other directions. The blood vessels, being acted upon both centrally and peripherally, are not affected equally, and it seems probable that those in the kidney are dilated disproportionately. Coupled with faster pulse and normal or increased pressure, this results in a greater renal supply of blood and enhanced glomerular filtration because of increased flow, and rise of glomerular capillary pressure, due to vascular adjustments within the kidney.

Other physiologic effects are of lesser importance. The acid gastric secretion is increased, especially with more than the usual doses, and this is synergistic with that caused by histamine or alcohol. The temperature is raised in proportion to the dose, from 0.5 to 1.2° F., and sometimes mild glycosuria is caused in animals. The products of normal metabolism may be altered in other ways, but this is not of great significance during clinical administration.

The toxicology of caffeine is not very important, although therapeutic amounts

may sometimes cause untoward symptoms in susceptible persons. Larger doses may produce excitement, vertigo, tremors, nausea, frequent urination, palpitation, ringing in the ears, delirium and sometimes convulsions. The fatal dose is so high, presumably about 10 grams, that recovery is practically always the rule, even when the symptoms were violent. The treatment by means of evacuation and narcotics is usually sufficient to bring about recovery in 24 hours, but some restlessness and weakness may persist for some time.

In this connection, it might be well to note the time-honored question about comparative harm from the caffeine-containing beverages. Tea contains 2-3 per cent, coffee about 1.2 per cent, yet a cupful of prepared drink has about 0.06 gram in each case because of the differing amounts used. From the quantity of caffeine, therefore, tea and coffee should be equally harmful, but it is very doubtful if any of the untoward results to habitual drinkers can be attributed to the compound. The tannin of green tea is constipative, while the caffeo of coffee is somewhat laxative, and other compounds are undoubtedly concerned in the results.

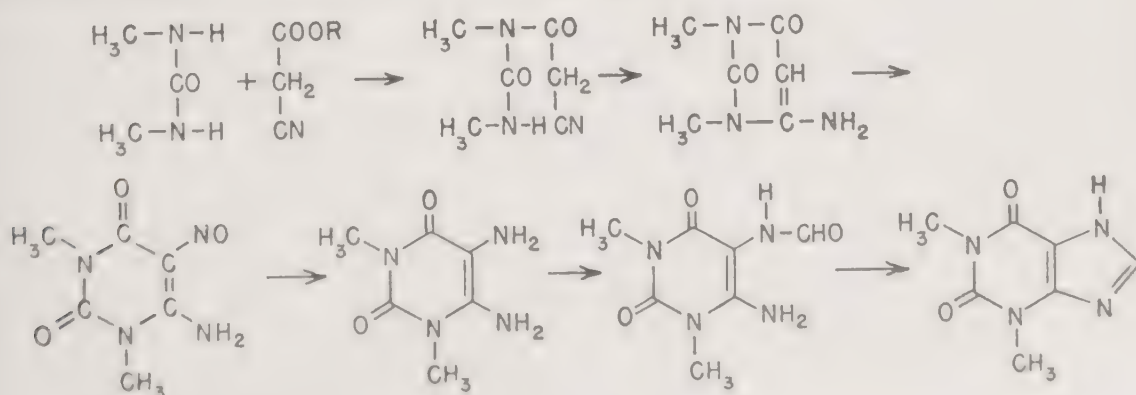
The therapeutic uses of caffeine have already been indicated in part. It is often employed in headaches of certain kinds, such as in neuralgia, rheumatism, migraine and in those due to fatigue, most often combined with other analgetics, especially acetanilid, phenacetin, aspirin or aminopyrine. It is given as an efficient diuretic especially in

cardiac edema, but is usually inactive or harmful in the presence of renal disease. It is an effective antidote against poisoning by narcotics such as morphine, usually being presented in such cases in the form of black coffee. Sometimes it is useful as respiratory or circulatory stimulant, mostly as adjuvant to other agents. Occasionally it may be employed to increase gastric secretion.

The official dose is 0.2 gram.

OFFICIAL OCCURRENCE	PER CENT CAFFEINE
U.S.P.	
Caffeine and Sodium Benzoate.....	47-50
Caffeine and Sodium Benzoate Injection	
Citrated Caffeine	48-52
N.F.	
Caffeine and Sodium Salicylate.....	48-52

Theophylline U.S.P. (Theocin), 1,3-dimethylxanthine, occurs as a white, odorless, crystalline powder that has a bitter taste and is stable in the air. It is sparingly soluble in water (1:120) and in alcohol (1:80), but it is more soluble in hot water and freely so in solutions of alkali hydroxides and in ammonia. With tannic acid it behaves as does caffeine, and it also gives the murexide test. Theophylline occurs in tea in small amount but is mostly prepared synthetically from ethyl cyanoacetate and symmetrical dimethylurea. These are condensed to aminodimethyluracil through an intermediate cyanacetyldimethylurea, then the product is converted to an isonitroso compound by nitrous acid and reduced to the amine. The latter with formic acid is converted to theophylline through a formyl derivative.



The central action of theophylline is not so powerful as that of caffeine, but the peripheral effects, and especially the diuresis, are much greater. It is now usually employed in the form of aminophylline as a diuretic, to dilate the coronary artery, to relax the bronchi in asthmatic conditions and to counteract myocardial infarction.

The official dose is 0.2 gram, and this may be used 3-4 times daily.

OFFICIAL OCCURRENCE	PER CENT THEOPHYLLINE
U.S.P.	
Theophylline and Sodium Acetate.	55-65

Aminophylline (Theophylline Ethylenediamine) U.S.P. "contains not less than 75 per cent and not more than 82 per cent of anhydrous theophylline ($C_7H_8N_4O_2$) and not less than 12.3 per cent and not more than 13.8 per cent of ethylenediamine $C_2H_4(NH_2)_2$." It consists of white or slightly yellowish granules or powder with a slight ammoniacal odor and a bitter taste, and it gradually absorbs carbon dioxide from the air with liberation of free theophylline. It is soluble in water (1:5) to give an alkaline solution that may become turbid on standing. It is the agent of choice when the therapeutic effect of theophylline is desired. The official dose is 0.2 gram orally, 0.25 gram intravenously or intramuscularly.

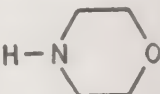
OFFICIAL OCCURRENCE
U.S.P.
Aminophylline Injection

Theobromine, 3,7-dimethylxanthine, consists of colorless needles or a white, odorless, crystalline powder that is only slightly soluble in water but dissolves readily in alkalies. It is generally extracted from waste products of the cocoa and chocolate industry; it is contained in the beans to the extent of 0.5-3.0 per cent. It is much less potent than theophylline but may be used for the same purposes, and it is considered preferable for long-continued treatment. It is used in the form of salt combinations, for which the dose is 0.5-1.0 gram.

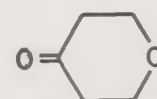
OFFICIAL OCCURRENCE	PER CENT THEOBROMINE
U.S.P.	
Theobromine and Sodium Acetate	55-65
Theobromine and Sodium Acetate Capsules	
N.F.	
Theobromine and Sodium Salicylate	46.5

OTHER RING SYSTEMS

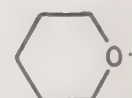
Of the hundreds of other ring systems containing hetero atoms, very few are of any pharmaceutical importance at the present time. Some representative compounds from them are used industrially, and some are of significance in plants or animals. An

example of these is morpholine, $H-N$ 

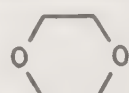
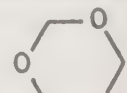
which is much employed as a solvent in emulsions and floor polishes and in boilers to prevent corrosion. The derivatives of

pyrone,  occur commonly

in plants, for example, meconic acid and chelidonic acid, and are especially of interest in the flavones, in the xanthenes and in the anthocyanidins which are the coloring matters in flowers. Tocopherol (vitamin

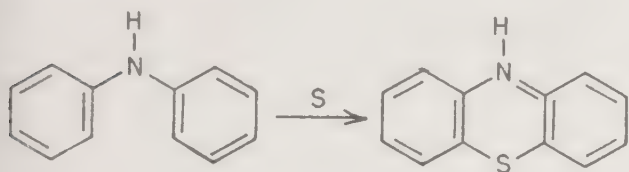
E) is a derivative of pyrane, .

Rotenone from derris root, cannabidol from cannabis and hematoxylin from logwood are other illustrations. In addition, dioxane from ethylene glycol and trioxane from formal-

dehyde,  and , as well as paraldehyde, which is a trimethyl derivative of the latter, are well known.

Phenothiazine (Thiodiphenylamine) N.F. occurs as a pale greenish-yellow to dark greenish-gray powder, granules or flakes. It is tasteless, has a slight characteristic odor and is slowly oxidized in the air to become darker in color. It is insoluble in water but will dissolve in alcohol (1:75) and in acetone (1:5). With ferric chloride

in alcoholic solution it gives a green color, and with hydrogen peroxide in acid solution gives a deep red color. It is made by fusing together diphenylamine and sulfur at 180° C. in the presence of a small amount of iodine as catalyst.



It is the parent of the thiazine dyes, of which methylene blue is a characteristic member.

Phenothiazine was first employed as an insecticide and is still highly regarded for this purpose. Later it was shown that thionol, formed as an oxidation product in the body, is actively bactericidal in either acid or alkaline media but not in neutral solution. Good results were reported in using phenothiazine for infections of the urinary tract, using doses of 1.3-2.0 grams by mouth, but there may be toxic reactions, such as secondary anemia, abdominal cramps, hematuria and signs of liver damage.

It is used chiefly as an anthelmintic in animals, where it is apparently almost indispensable because of the number of parasites for which it is effective. These include most of the species that inhabit horses, cattle, sheep, swine and fowl, but the worms of dogs and cats are not usually affected sufficiently. Untoward reactions are not uncommon, especially in horses and swine or young and weak animals. The official doses are: for horses and mules, 30-50 grams; for cattle, 50-80 grams; for calves, 24-40 grams; for swine, 4-30 grams; for sheep and goats (up to 60 pounds), 15 grams and for chickens, 0.5 gram.

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Dyes

TRIPHENYLMETHANE DYES

PHTHALEIN DYES

AZO DYES

ACRIDINE DYES

MISCELLANEOUS DYES

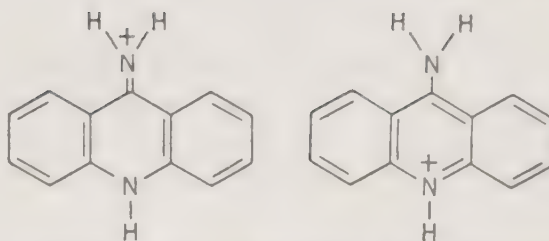
Dyes are colored compounds that adhere to cloth, paper, leather or other materials and retain their original appearance after exposure to light, air and washing. Compounds are colored when they absorb light within the range of the visible spectrum i.e., from 4000 to 7500 Å (Å=angstrom unit = 10^{-8} cm.). All compounds absorb light of some wave-length but most of them absorb only in the ultraviolet (1,500–4,000 Å) and infrared regions (7,500–250,000 Å), thus are not colored. The region in which a compound absorbs depends on the vibrational and rotational frequencies of the atoms and electrons which make up the compound, only that light being absorbed which corresponds to the natural frequencies of the molecule. Atoms are so heavy that their frequencies come in the infrared. The frequencies of electrons in most cases fall in the ultraviolet. It is only when the electrons are loosely held

in the molecule that their frequencies are slow enough for them to absorb light in the visible.

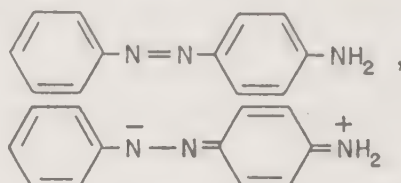
For many years it has been known¹ that groups such as C=C, C=S, N=N, etc., called chromophores, were always present in colored compounds. In addition to the chromophores, another type of group called auxochrome and represented by NH₂, SO₃H, etc., was also always present in dyes. To the auxochromes was attributed the ability of the dye to attach itself to the material being dyed by reacting with the acid or basic groups in this material. They also were observed to influence the intensity and sometimes the shade of the color.

A further understanding developed when it was realized that virtually all dyes and colored compounds are resonating molecules² to which more than one valence bond structure must be assigned to adequately describe the structure of the molecule. In

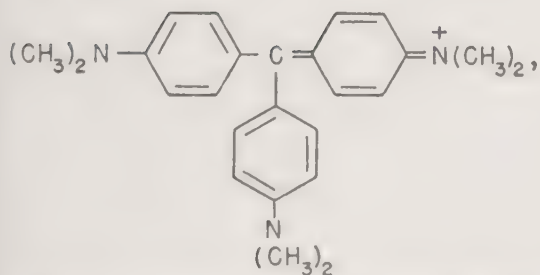
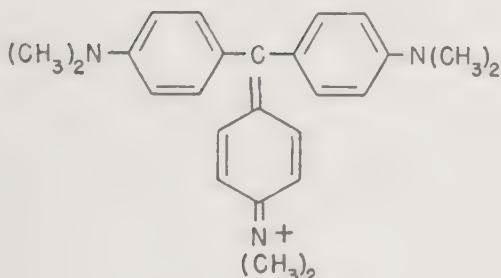
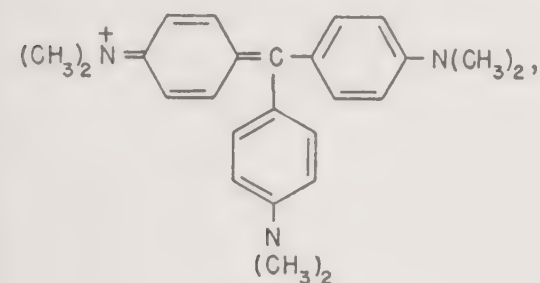
many, but not necessarily all cases, resonance is associated with the electrons being held with less constraint, thus slowing down their vibration frequencies and permitting visible light to be absorbed by the compound. With the triphenylmethane, diphenylmethane and acridine dyes, the resonating forms involve a shift of a positive charge to different positions within the molecule. With the phthaleins, a negative charge is so shifted. The azo dyes involve resonance between a normal neutral form and one or more forms involving a separation of charge.



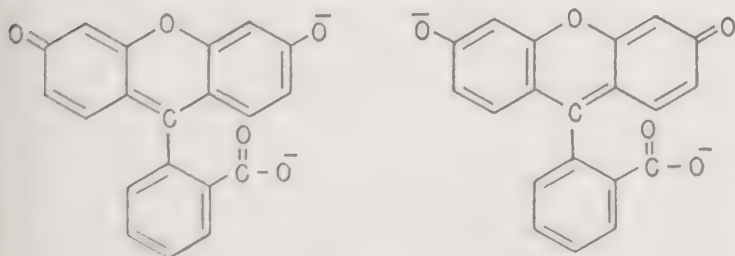
Resonating forms of the cation of 9-aminoacridine



Resonating forms of the undissociated molecule of aniline yellow



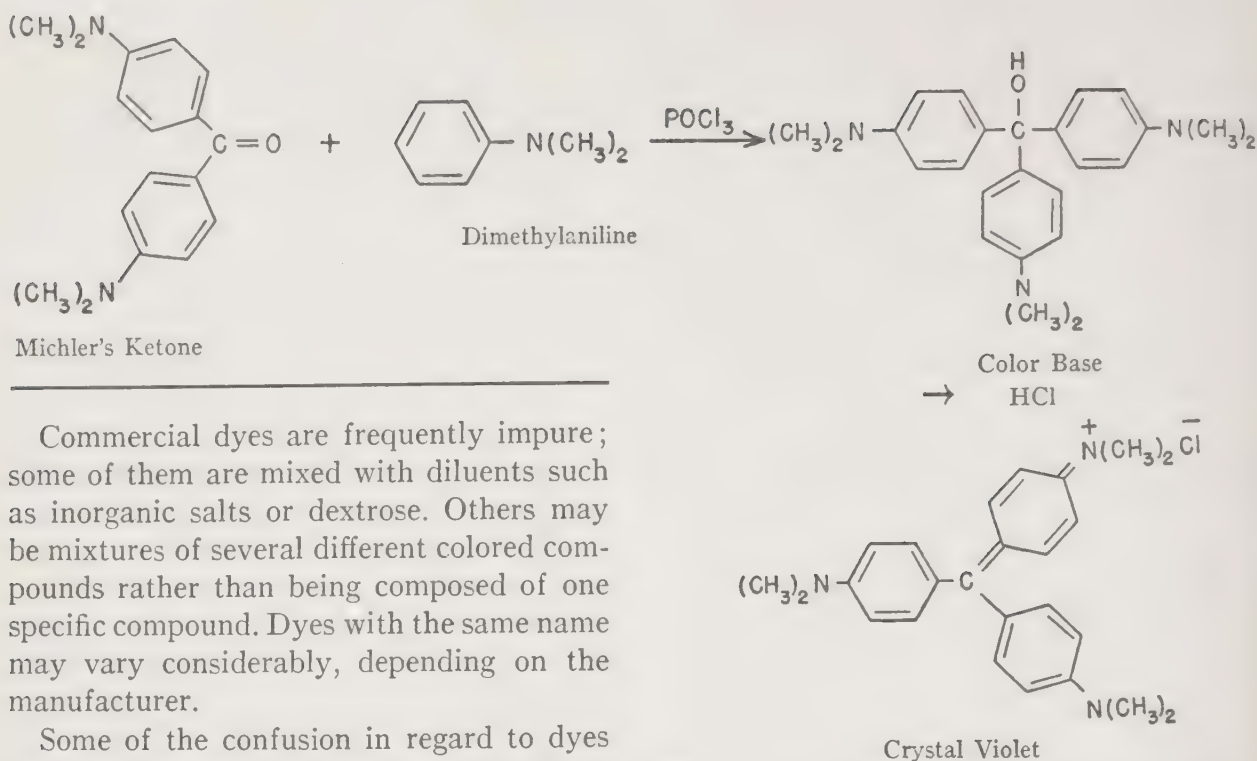
Resonating forms of the cation of crystal violet



Resonating forms of the anion of fluorescein

More recently it has been shown,³ using the concept of resonance, that the triphenylmethane, diphenylmethane, xanthene, acridine, diphenylamine, oxazine, thiazine and azine dyes can be brought together into one family and that the wave-length of maximum absorption for these compounds can be predicted within 3 mμ.

The discovery that some dyes would stain certain tissues and not others led Ehrlich to the idea that dyes might be found that would selectively stain, combine with and destroy pathogenic organisms without causing appreciable harm to the host. He and other workers studied a number of dyes with this idea in view and, as a result of these studies, some azo, thiazine, triphenylmethane and acridine dyes came into use as antiseptics, trypanocides, etc. However, there appears to be no correlation between the dyeing properties of a series of compounds and their antiseptic or bacteriostatic properties.



Commercial dyes are frequently impure; some of them are mixed with diluents such as inorganic salts or dextrose. Others may be mixtures of several different colored compounds rather than being composed of one specific compound. Dyes with the same name may vary considerably, depending on the manufacturer.

Some of the confusion in regard to dyes has been removed by standards set up by several official bodies. All dyes used in coloring pharmaceutical products and foods must conform to the Coal Tar Color Regulations established by the United States Food, Drug and Cosmetic Act. Standards for medicinal dyes and food colors are also sanctioned by the United States Pharmacopœa, the National Formulary and the Dye Certification Division of the United States Department of Agriculture. At present there are 18 dyes that are permitted to be used for the coloring of foods, providing the dye batch has been certified by the Food and Drug Administration. These dyes also may be used to color drugs and cosmetics. In addition to these, there are 66 dyes that may be used in drugs and cosmetics but not in foods and 29 dyes that may be used only in externally applied drugs and cosmetics.

TRIPHENYLMETHANE DYES

Methylrosaniline Chloride (Gentian Violet, Methyl Violet, Crystal Violet) U.S.P., (Gentian Violet Medicinal) N.N.R. "Methylrosaniline chloride is hexamethylpararosaniline chloride usually admixed with pentamethylpararosaniline chloride and tetramethylpararosaniline chloride." Some

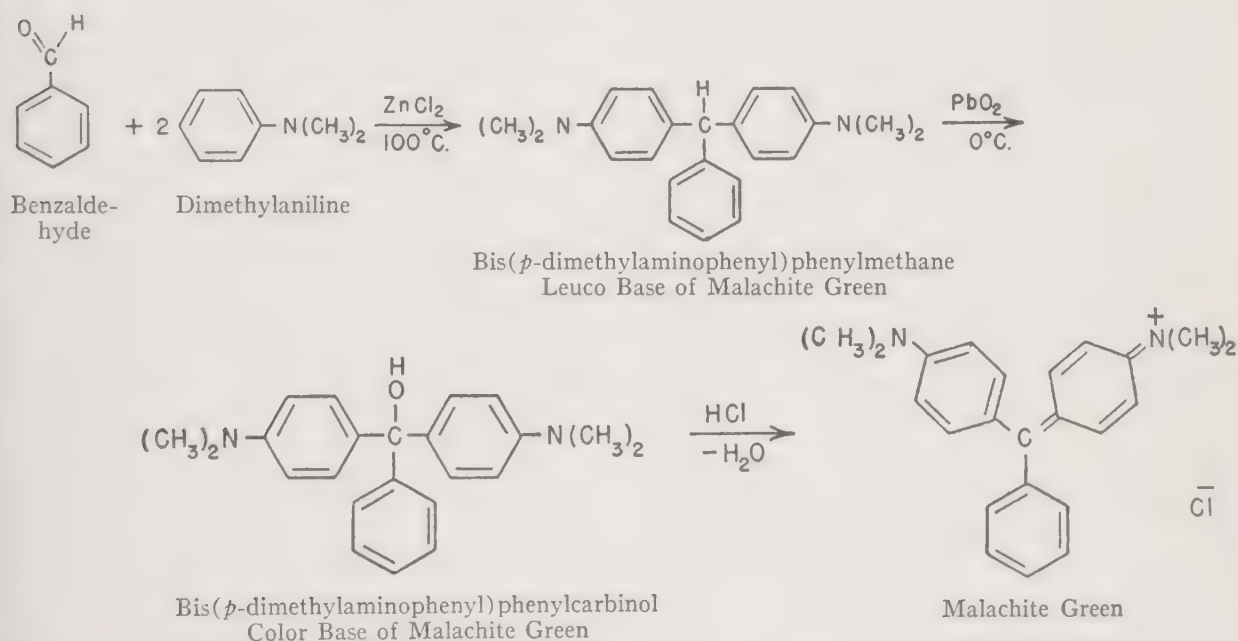
of the methyl violets of commerce have methyl groups substituted in the ring and there is considerable lack of uniformity in composition of those being distributed commercially. The pure synthetic crystal violet is presumably free of nuclear methyl groups.

Crystal violet may be prepared by the reactions indicated above.

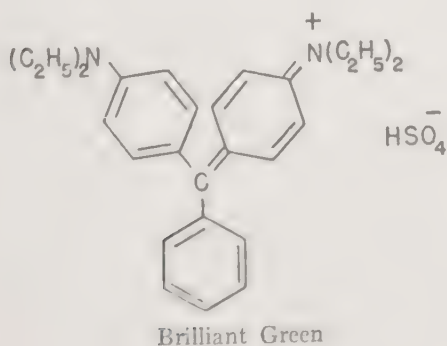
Methylrosaniline chloride occurs as a green powder or as green particles with a metallic luster. The commercial dye frequently contains dextrose and other diluents and should not be used medicinally. It is soluble in water (1:35), in alcohol (1:10) and in glycerine (1:15) but it is insoluble in ether. The dye is much more effective against gram positive organisms than against gram negative organisms. It has been used as an antiseptic for wounds, mucous membranes and as a treatment for burns. It has also been used in treating arthritis, empyema and *Strongyloides* infestation.

OFFICIAL OCCURRENCE	PER CENT METHYL ROSANILINE CHLORIDE
N.F.	
Methylrosaniline Chloride	
Jelly	1.0
Methylrosaniline Chloride	
Solution	1.0

Malachite Green (Tetramethyl-di-*p*-amino-triphenylcarbinol chloride) is a green crystalline powder soluble in water and alcohol. The commercial dye is used in the form of the ZnCl_2 double salt. Only the zinc-free compound should be used medicinally. It has been used in a one per cent ointment for the treatment of impetigo and ulcers, in a 1:1,000 water solution as a wound antiseptic and 1:2,000 in normal saline solution by subcutaneous injection for the treatment of trypanosomiasis. The usual method for the preparation of malachite green is as follows:



Brilliant Green (Tetraethyldiaminotriphenylcarbinol Anhydride Sulfate) N.N.R. is a green crystalline powder, soluble in alcohol (1:20) and in water (1:20). It is a homologue of malachite green and can be prepared in the same way by substituting diethylaniline for dimethylaniline.

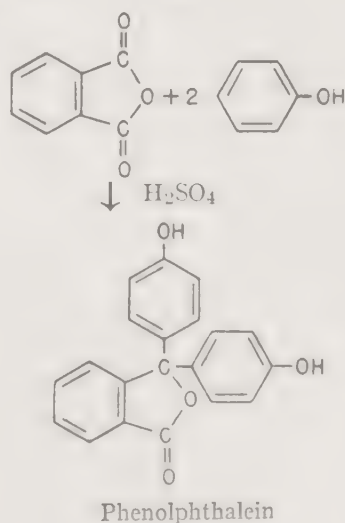


It is used as a surgical antiseptic in a 1:1,000 solution. It is said to promote epithelization. It is employed as a one to two per cent ointment in the treatment of sluggish ulcers and is a component of Dymixal, commonly known as the "Aldrich" or "Triple Dye" mixture.

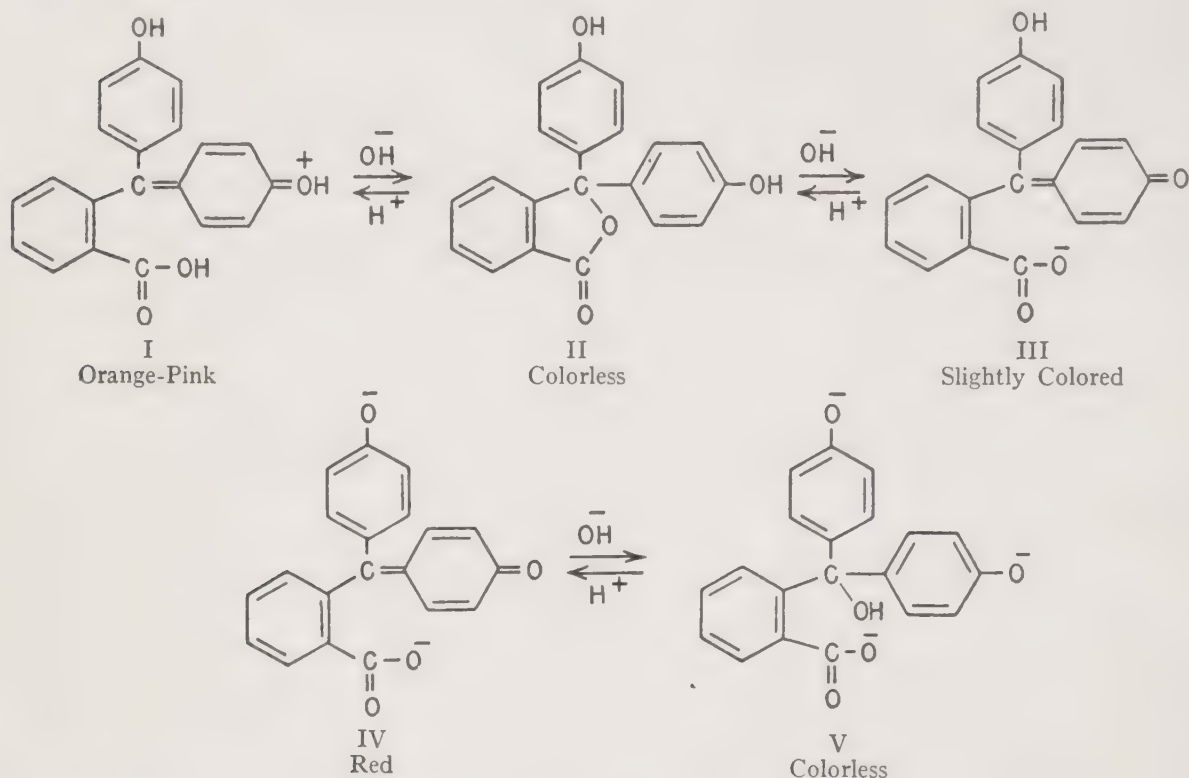
PHTHALEIN DYES

Phenolphthalein U.S.P. is a white or faintly yellowish-white, crystalline powder. It is soluble in alcohol (1:15), in ether (1:100) and in dilute bases but is almost

insoluble in water. It can be made by condensing phenol with phthalic anhydride.



Phenolphthalein is one of the most commonly used indicators for the titration of weak acids with alkali. It can exist as a neutral molecule and as four different ions, depending on the pH.



The color change from colorless to red which takes place in the pH range 8.3 to 10.0 is the one employed in titrating weak acids. This involves a change from the colorless molecule II to the red divalent ion IV. That phenolphthalein becomes colorless in strong base due to the conversion to the trivalent ion V or that it turns orange-pink in very strong acid due to formation of the monovalent positive ion I, is not so generally known. Both of the colored ions have a form of comparable energy in which the positive charge in I or the negative charge in IV is on the other phenolic oxygen. The structure is said to resonate between the two forms, as is the case with many colored organic molecules or ions. To have resonance, it is necessary that the forms differ only in their electronic configuration. If an atom has to shift to go from one form to another, it is no longer a state of resonance but involves tautomerism or a rearrangement.

Phenolphthalein is used as a mild, tasteless laxative in the treatment of constipation. The colorless or almost colorless U.S.P. product has only about one third the laxative

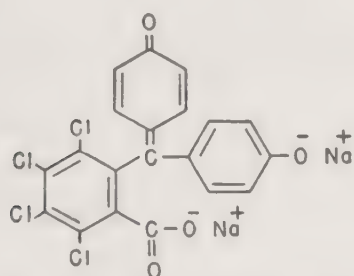
action of yellow phenolphthalein, a more impure product. It was thought for some time that the greater laxative action of the yellow product was due to hydroxyanthraquinones which were presumed to have been formed during the synthesis. Recent work has shown,⁴ however, that hydroxyanthraquinones are not present in yellow phenolphthalein nor is the laxative action of U.S.P. phenolphthalein increased by adding hydroxyanthraquinones to it. A number of colorless compounds have been isolated from the yellow product; these include fluoran, isophenolphthalein [3-*o*-hydroxy-phenyl-3-*p*-hydroxyphenyl]phthalide], phenolphthalin, 2-(4-hydroxybenzoyl)-benzoic acid and other compounds not yet identified. None of these compounds showed a laxative action greater than that of U.S.P. phenolphthalein. The cause of the greater laxative action of

yellow phenolphthalein over that of the colorless compound is still undetermined.

It may be combined with other drugs such as agar-agar or mineral oil. Phenolphthalein is not well-absorbed from the intestinal tract and has a low toxicity. It is found in many of the commercial laxative preparations.

The average dose is 60 mg.

Phenoltetrachlorophthalein N.N.R. is used for testing the functional activity of the liver. Solutions of the disodium salt have a relatively high pH and although they may

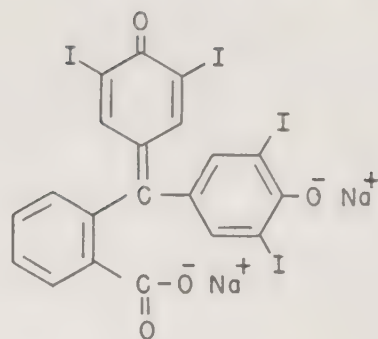


Phenoltetrachlorophthalein Sodium

be given intravenously, are not suitable for subcutaneous or intramuscular injection. The solutions absorb carbon dioxide from the air, with the resulting precipitation of the free acid, so they should not be exposed to the atmosphere for too long a time. Sodium salts of phthaleins are also incompatible with high molecular weight quaternary ammonium salts such as Zephiran, Phemerol, etc., due to the mutual precipitation of the high molecular weight ions as insoluble salts. The free acids of the phthaleins are quite insoluble and so the sodium phthaleins are precipitated by all acidic substances. Phenoltetrachlorophthalein largely has been replaced by other compounds for the hepatic function test.

The dose is 5 mg. per kg. of body weight.

Iodophthalein Sodium (Soluble Iodophthalein, Tetraiodophenolphthalein Sodium, Tetraiodophthalein Sodium, Tetiophthalein Sodium) U.S.P. (Iodeikon) is the disodium salt of tetraiodophenolphthalein. It is a blue-violet, odorless, crystalline powder having a saline taste. It is freely soluble in water (1:7) and is slightly soluble in

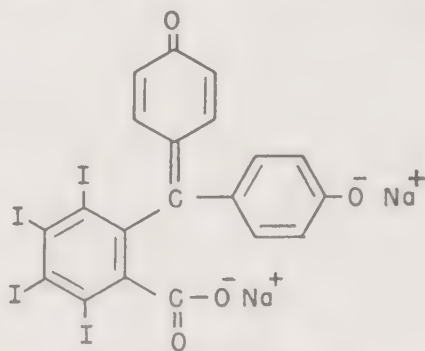


Iodophthalein Sodium

alcohol. It is employed as a test for liver function and for the roentgenologic examination of the gall bladder. The compound is administered by intravenous injection and under normal conditions, is concentrated in the gall bladder in sufficient amounts to be opaque to the x-rays. The opacity of atoms to x-rays is a function of the weight of the atoms. The four heavy iodine atoms substituted in phenolphthalein make the compound opaque to x-rays. In cases of impaired liver function, the compound is retained in the blood and the amount so retained is a measure of the extent of the liver dysfunction.

The average dose for each 10 kilograms of body weight is 0.5 Gm. orally and 0.3 Gm. intravenously.

Phentetiothalein Sodium N.N.R. (Phenoltetraiodophthalein sodium, Disodium phenoltetraiodophthalein, Iso-iodeikon) occurs as bronze-purple, odorless, hygroscopic granules that are soluble in water and alcohol.

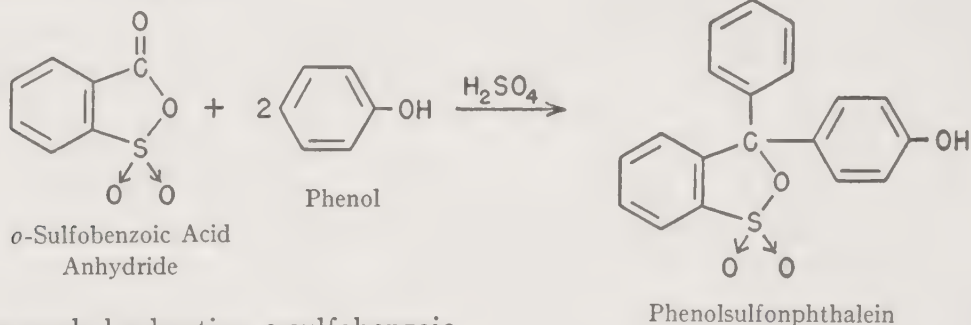


Phentetiothalein Sodium

It is used for the simultaneous test of hepatic function and the roentgenologic examination of the gall bladder.

The dose is 40 mg. per kilogram of body weight intravenously.

Phenolsulfonphthalein U.S.P. (Phenol red) is a red, crystalline powder that is stable in air. It is soluble in water (1:1,300), in alcohol (1:350) and almost insoluble in ether. It dissolves readily in bases. This compound may be considered as a derivative of phenolphthalein in which the CO group is replaced by an SO₂ group.



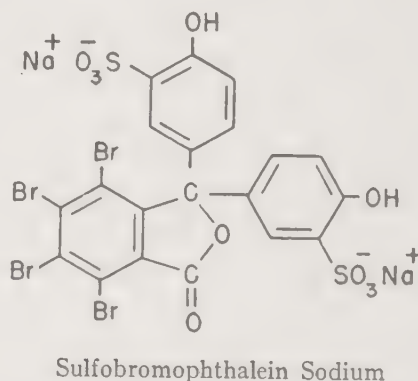
It can be made by heating *o*-sulfobenzoic acid anhydride and phenol in the presence of sulfuric acid. It is used as an indicator in determining hydrogen ion concentrations. The dye is employed as a diagnostic agent for determining renal function. For this purpose, the mono-sodium salt is injected intravenously or intramuscularly and the amount of phenolsulfophthalein excreted in the urine is measured quantitatively. When the kidney function is normal, the dye is excreted in a shorter time interval than when the kidney function is impaired.

The average diagnostic dose is 6 mg.

way of the liver. The introduction of sulfonic acid groups into compounds of this type decreases the toxicity and greatly increases the water solubility. The compound is injected intravenously, as a five per cent solution, and the amount remaining in the blood after a certain time interval is determined colorimetrically. The rate at which the dye is

removed from the blood is a measure of the hepatic function.

Normally this diagnostic agent is used



in doses of 5 mg. per kg. (1 cc. of the five per cent solution for each 10 kg. or 22 pounds of body weight). The concentration of the dye in the blood stream then is measured at the end of one hour and at regular time intervals thereafter in order to determine the rate of clearance.

OFFICIAL OCCURRENCE U.S.P.	PER CENT PHENOL- SULFOPHTHALEIN
Phenolsulfonphthalein Injection	0.6

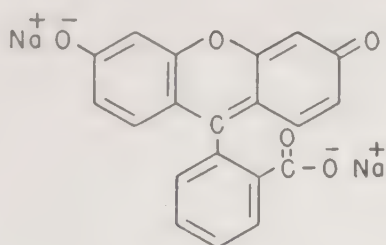
Sulfobromophthalein Sodium U.S.P. (Bromsulphalein Sodium, Disodium Phenoltetrabromophthalein Disulfonate) is a white, crystalline powder that has a bitter taste and is odorless. It is soluble in water but is insoluble in alcohol and acetone. It is hygroscopic.

Sulfobromophthalein sodium has largely replaced phenoltetrachlorophthalein for the determination of liver function. The bromine atoms in the compound cause it to be removed from the blood almost entirely by

OFFICIAL OCCURRENCE U.S.P.	PER CENT SULFOBROMO- PHTHALEIN SODIUM
Sulfobromophthalein Sodium Injection	5.0

Fluorescein Sodium (Soluble Fluorescein, Resorcinolphthalein Sodium) U.S.P.

is an orange, odorless, hygroscopic powder. It is soluble in water and sparingly soluble in alcohol.



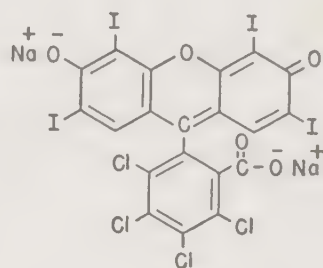
Fluorescein Sodium

The disodium salt forms highly fluorescent solutions when dissolved in water. The acidified solution has practically no fluorescence.

Fluorescein sodium is used as an ophthalmologic diagnostic agent. For this purpose, a solution consisting of 2 per cent of the dye and 3 per cent of sodium bicarbonate is employed. Diseased or abraded areas of the cornea, such as corneal ulcers, are stained green by the solution. Foreign bodies appear with a green ring around them, while the normal cornea is not stained. Loss of substance from the conjunctiva shows up as a yellow hue when treated with fluorescein sodium.

Rose Bengal (Tetraiodotetrachlorofluorescein) is made by reacting tetrachloro-

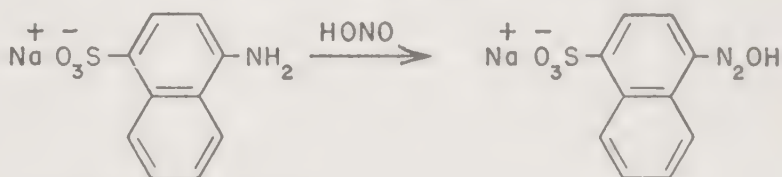
phthalic anhydride with resorcinol and iodinating the resulting product. It is used as a test for liver function. The liver almost exclusively removes the dye from the blood stream. From 100 to 150 mg. of the dye are injected intravenously in sterile saline. A normally functioning liver will remove 50 per cent of the dye within two minutes. The dye is photosensitive, so the dye, its solutions and the patients receiving it should be protected from light.



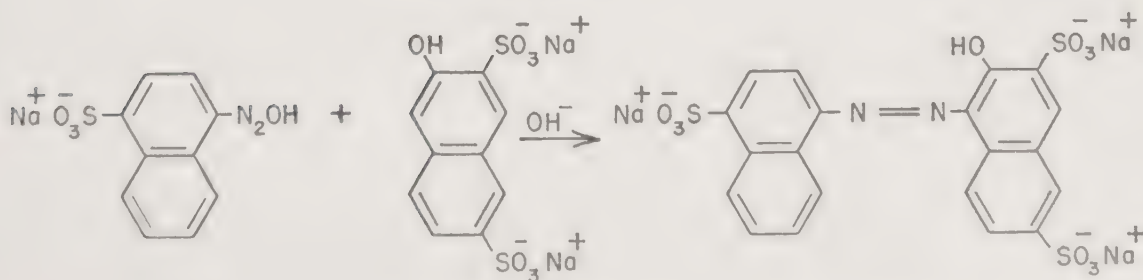
Rose Bengal

AZO DYES

Amaranth (F. D. and C. Red No. 2) U.S.P. [Trisodium salt of 1-(4-sulfo-1-naphthyl-azo) - 2 - naphthol-3, 6 - disulfonic acid] is a dark red-brown powder soluble in water (1:15) and very slightly soluble in alcohol. It is used to color pharmaceutical preparations and food products.



α -Naphthylamine-4-sulfonic
Acid Sodium Salt



β -Naphthol-3,6-disulfonic
Acid Disodium Salt

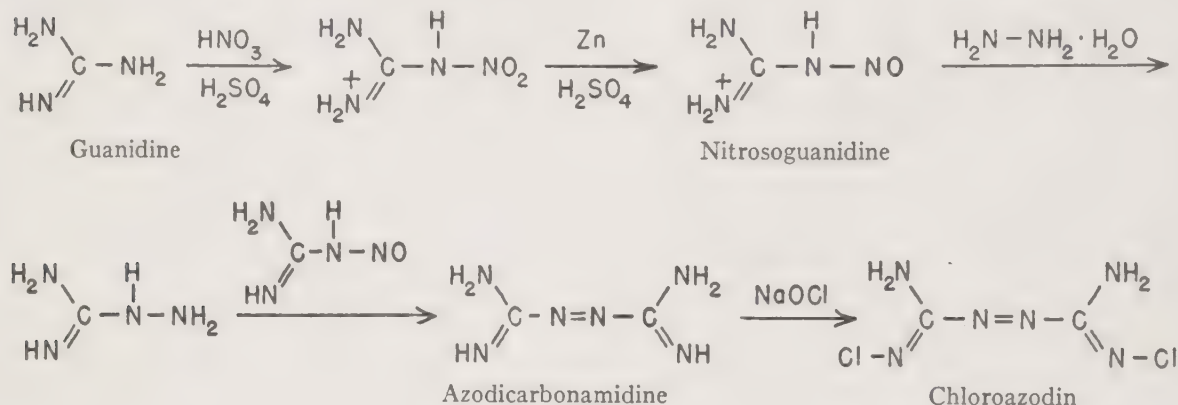
Amaranth

OFFICIAL OCCURRENCE
U.S.P.

PER CENT AMARANTH

Amaranth Solution 1.0

Chloroazodin U.S.P. (Azochloramide, N,N¹-Dichloroazodicarbonamidine) is a yellow, crystalline compound, slightly soluble in water, alcohol, vegetable oils and glycerol-triacetate.



The compound is reported to have a slow rate of hydrolysis in aqueous solution and to react slowly with organic matter and mild reducing agents. Its bactericidal action is said to be more prolonged and stronger in the presence of exudate and tissue fluids than other commonly used chloramines. It is used for wounds, 1:3,300 in an isotonic solution buffered at pH 7.4. A 1:2,000 solution in vegetable oil is used for application to the mucous membranes of the vagina and the rectum.

OFFICIAL OCCURRENCE
U.S.P.

PER CENT
CHLOROAZODIN

Chloroazodin Solution 0.26

Scarlet Red (Scarlet Red Medicinal, Biebrich Scarlet Red) N.F. (*o*-tolylazo-*o*-tolylazo- β -naphthol) is a dark-red, odorless powder. It is soluble (1:15) in chloroform, readily soluble in oils, fats and phenol, slightly soluble in alcohol, acetone and benzene and almost insoluble in water. The

compound is made by coupling diazotized *o*-aminoazotoluene with β -naphthol.

Scarlet red may be made according to the reactions at the bottom of the page.

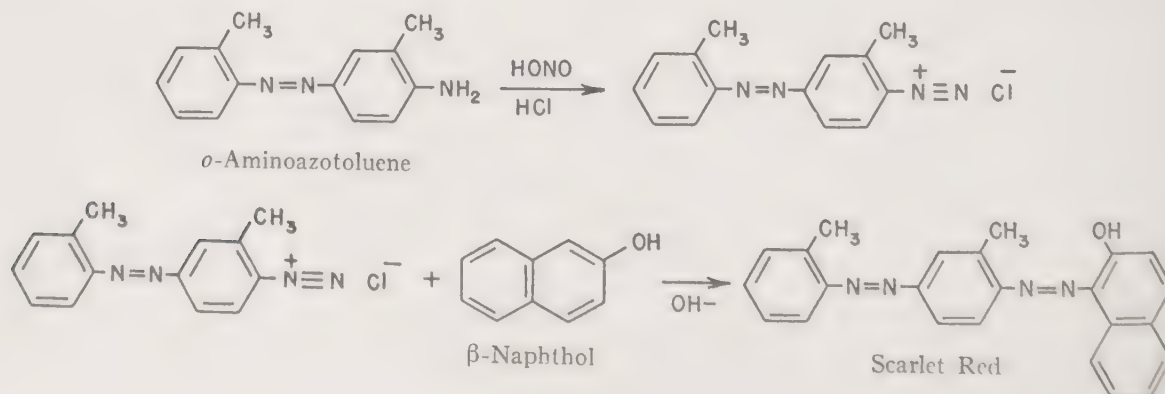
It is used to stimulate the growth of epithelial cells in wounds, burns and skin grafting. It usually is applied externally in about a five per cent ointment.

OFFICIAL OCCURRENCE
N.F.

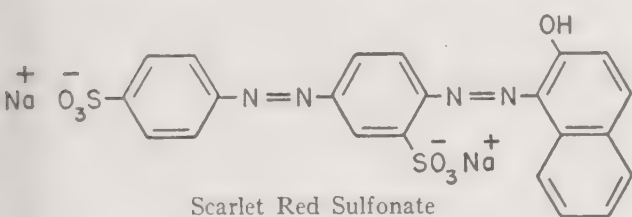
PER CENT SCARLET RED

Scarlet Red Ointment.. 5.0

Scarlet Red Sulfonate N.N.R. (Biebrich scarlet, Azobenzenedisulfonic acid azobeta-naphthol disodium salt) is a dark, brownish-red, odorless powder. It is soluble in water,



slightly soluble in alcohol, acetone and ether and almost insoluble in benzene, fixed oils, fats and petrolatum. It is used for the same conditions as scarlet red in the form of a five to ten per cent ointment or a four per cent emulsion. The dye may be prepared by coupling diazotized aminoazobenzene-3,4'-disulfonic acid with β -naphthol.

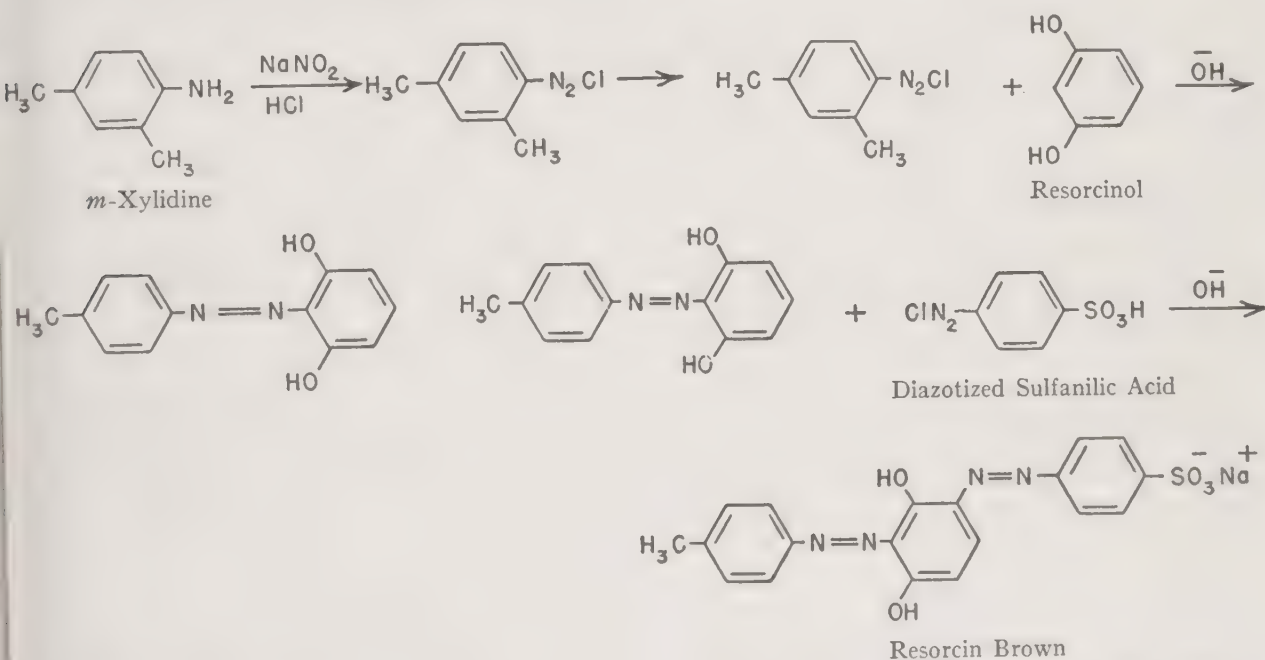


Dimazon, like the above two compounds, is used to stimulate the growth of epithelial cells. It is used as a two per cent solution in petrolatum ointment or in olive oil or as a five per cent powder mixed with talc.

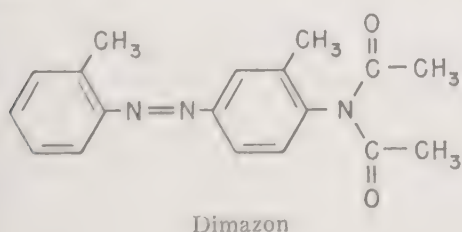
Resorcin Brown (D and C Brown No. 1) N.F. [Sodium 4-*p*-sulfonphenylazo-2-(2,4-xylylazo)-1,3-resorcinol] is a deep-brown powder, soluble in water, glycerin and alcohol, but sparingly soluble in ether and acetone.

Resorcin brown is used in coloring drugs and cosmetics.

Resorcin brown is made in the following way.



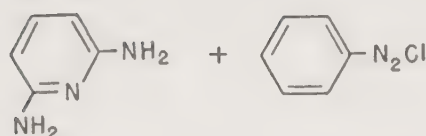
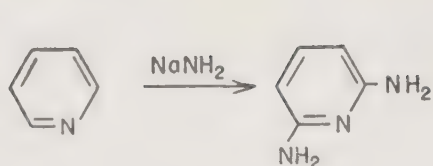
Dimazon (Pellidol, Diacetylaminoazotoluene) is an orange, crystalline powder, readily soluble in alcohol, ether, benzene and mineral oil, but insoluble in water. It is prepared by the acetylation of aminoazotoluene.



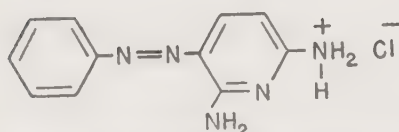
OFFICIAL OCCURRENCE	PER CENT RESORCIN BROWN
N.F.	
Resorcin Brown Solution.....	0.5

3-Phenylazo-2,6-Diaminopyridine Monohydrochloride (Pyridium, Mallophone) is a brick-red, fine, crystalline powder, prepared in the manner shown on the following page. It is readily soluble in hot water, alcohol or glycerol and slowly soluble in cold water.

It is employed as a genito-urinary anti-septic for pre-operative treatment in urologic operations and in conditions such as



↓ H⁺

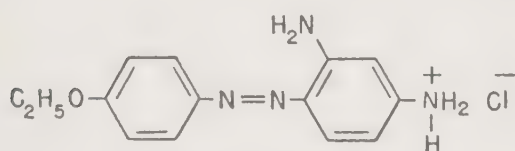


3-Phenolazo-2,6-diaminopyridine Monohydrochloride

prostatitis, vaginitis and cystitis. The oral dose is 0.2 Gm. usually given in tablet form. It is also used topically as a one per cent jelly or as a 0.1 per cent solution in water. The dye is said to be effective in either acid or alkaline urine.

Pyridium is incompatible with silver or mercury compounds, sulfur and sulfur compounds, mineral acids, chlorine water, Dakin's solution and tincture of iodine.

Ethoxazene (Serenium, 2,4-Diamino-4'-ethoxy-azobenzene hydrochloride) is a dark-red, slightly bitter powder, soluble in boiling water (1:100). It is used as a genito-urinary

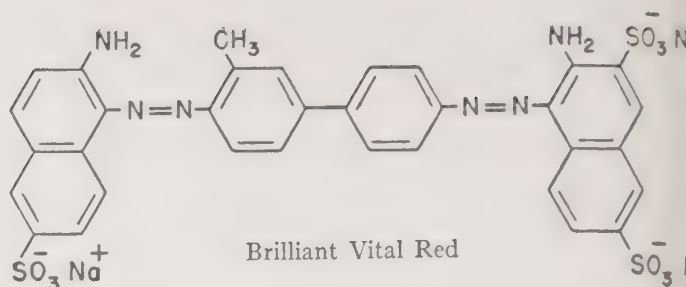


Ethoxazene

antiseptic for such conditions as pyelitis, cystitis and prostatitis. It is effective in acid or alkaline urine. It is administered orally, the dose being 0.1 Gm.

Brilliant Vital Red has the property of selectively staining tissues when introduced into living organisms, and, like other dyes having this property, is known as a vital stain.

It is used therapeutically as an adjunct in the treatment of convulsive states and

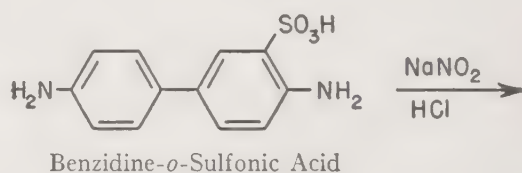


Brilliant Vital Red

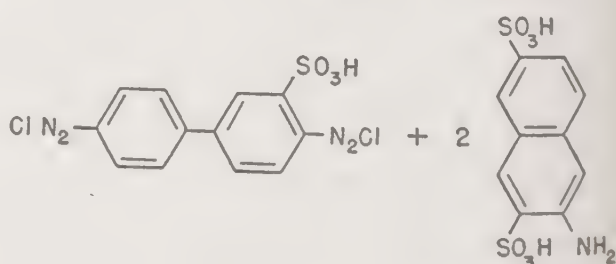
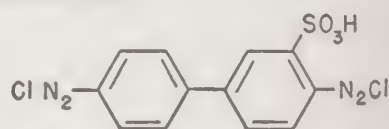
post-traumatic head conditions and at present, is being tried experimentally in the treatment of degenerative diseases of the central nervous system.

Trypan Red was first introduced by Ehrlich in 1904 as a trypanocidal agent but is no longer used for this purpose. It is a vital stain and is used therapeutically as an adjunct for relief of symptoms associated with the convulsive state and post-traumatic head conditions.

Trypan red is made as follows.

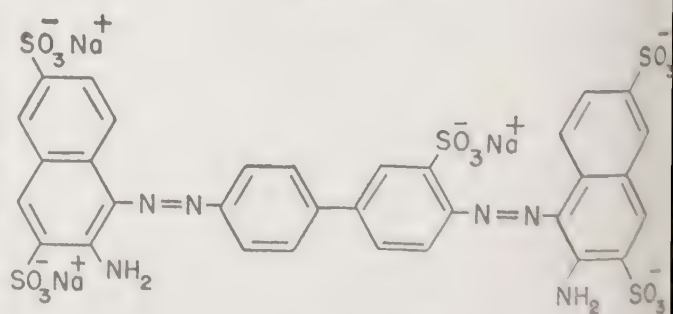


Benzidine-o-Sulfonic Acid



2-Naphthylamine-3,6-Disulfonic Acid

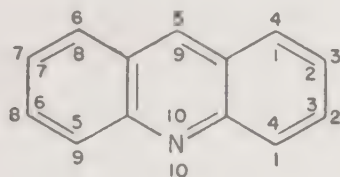
↓ NaOH



Trypan Red

ACRIDINE DYES

Acridine has the same relation to anthracene that pyridine has to benzene. It may be considered as derived from anthracene if one of the middle CH groups is replaced by nitrogen. The numbering on the inside of the formula is that used by Chemical Ab-



Acridine

stracts, the outside numbers are those employed by the British and also the N.F. in this country. Thus, 9-aminoacridine in the Chemical Abstracts system and 5-aminoacridine in the British system are the same compound. The system used here is that adopted by Chemical Abstracts.

Browning was the first to observe (in 1912) that one of the aminoacridines "Trypaflavine" (later called Acriflavine) was active against trypanosomes. The next year, this compound and proflavine were introduced as general antiseptics and were used extensively in World War I. In 1923, Rivanol, a diaminoethoxy derivative, was introduced. The work of Albert, Rubbo and co-workers⁵ on the acridines has led to the discovery that the antibacterial action of these compounds is proportional to the extent to which they are ionized at the biologic pH value 7.3. Evidence also was presented that the cations of the acridine derivatives injure the bacteria by competing with the hydrogen ion, which functions as an essential bacterial cation. As a result of this work, 9-aminoacridine has come into use as an externally applied, nonstaining antibacterial agent. It is not useful for injection, however, because it is precipitated by saline solutions. Recently, 4-methyl-9-aminoacridine was introduced as an acridine derivative that is compatible with physiologic saline solution and therefore has the possibility of being used by injection. Most of the acridines,

however, have a necrotic and inflammatory action on tissues and so are not used intramuscularly or subcutaneously. The aminoacridines maintain their activity in the presence of pus and the body fluids and are claimed to interfere very little with the healing process. However, acriflavine is said to inhibit leucocytic activity in concentrations of 20 per cent of that required to inhibit the growth of bacteria in the blood stream. Due to the fact that they, like most cations, are not nearly as active in acid solution as in neutral or basic surroundings, they are effective urinary antiseptics only if the urine is basic. The reason for this is presumably their mode of action, which involves a competition with hydrogen ion. The greater the concentration (law of mass action) of hydrogen ions, the less chance the aminoacridine ions have of displacing the hydrogen ions.

Since some of these compounds have high activity against gram negative organisms and are more active than the sulfonamides against gram positive organisms, they may possibly come into more extensive use.

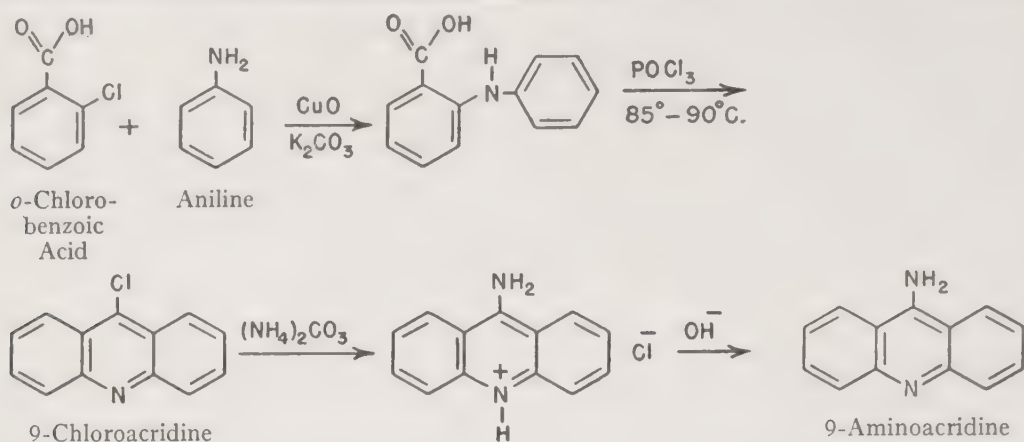
9-Aminoacridine Hydrochloride (5-Aminoacridine hydrochloride, Monacrin, Acramine yellow) is a pale-yellow, crystalline, bitter, odorless powder. It is soluble in water (1:300), in 90 per cent alcohol (1:150) and in glycerol (1:55).

The following synthesis of 9-aminoacridine (p. 334) serves to illustrate the synthesis of the acridine antibacterial agents.

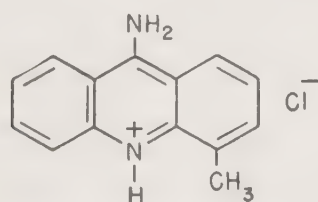
The compound is incompatible with acids, alkalis and chlorides. It is not suitable for injection partially because of the chloride incompatibility, but it is an effective bacteriostatic and bacteriocidal agent for topical application.

The bacteriostatic activity of the sulfonamides is greatly enhanced when used with 9-aminoacridine. There is approximately a tenfold increase in the activity with the mixed drugs.

9-Amino-4-Methylacridine Hydrochloride (5-Amino-1-methylacridine, Neomonoacrin, Salacrin) is a yellow, crystalline, bit-



ter powder that is not affected by light. It is soluble in water (1:220) and in absolute alcohol (1:380). Dilute solutions of the compound exhibit a strong blue fluorescence. This compound is one of the least toxic of

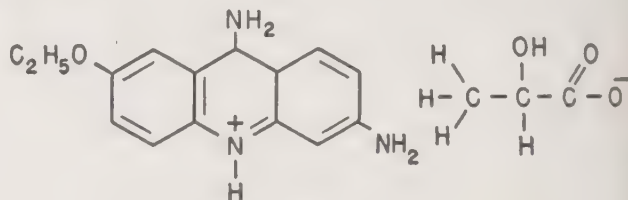


4-Methyl-9-aminoacridine
Hydrochloride

some 30 9-aminoacridine derivatives that have been tested. It is nonstaining to skin, is a more active antibacterial agent than 9-aminoacridine and is compatible with physiologic saline solution.

Rivanol (3,9-Diamino-7-ethoxy acridine

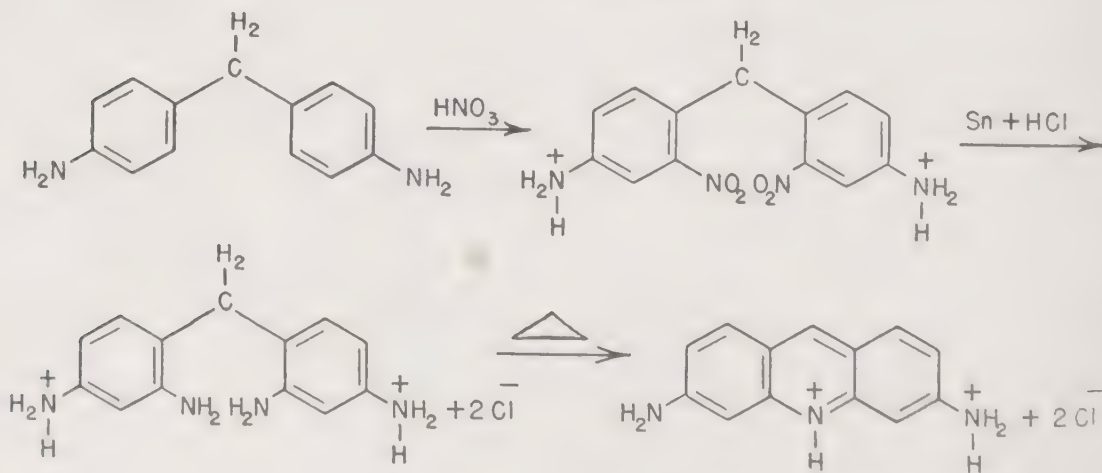
lactate) is a yellow compound, soluble in water (1:15). It is used in the treatment of human dysenteries and streptomastitis in cows.



Rivanol

Proflavine Dihydrochloride, N.F. (3,6-Diaminoacridine dihydrochloride), occurs as orange-red to brownish-red, odorless crystals. It is soluble in water and very slightly soluble in liquid petrolatum, ether and chloroform. It is sensitive to light. The water solutions sometimes become turbid, in which case they should be discarded.

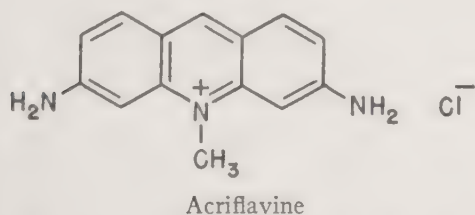
Proflavine can be made in the following manner.



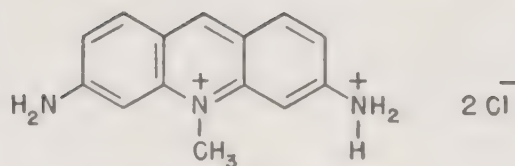
Proflavine Dihydrochloride

Proflavine Sulfate N.F. (3,6-Diamino-acridine sulfate) occurs as a reddish-brown, odorless powder. It is affected by light and is less soluble in water (1:300) than the corresponding dihydrochloride. It is slightly soluble in alcohol and nearly insoluble in ether, liquid petrolatum and chloroform.

Acriflavine (Acriflavine Base, Neutral Acriflavine) N.F. (3,6-Diamino-10-methylacridinium chloride) is a deep-orange, odorless, granular powder. It is soluble in water (1:3), sparingly soluble in alcohol and nearly insoluble in ether and chloroform. Its solutions exhibit a marked fluorescence and are sensitive to light. The commercial medicinal product is mixed with 3,6-diamino-acridine. Because this compound is more nearly neutral, it is less irritating to tissues than the acriflavine hydrochloride.

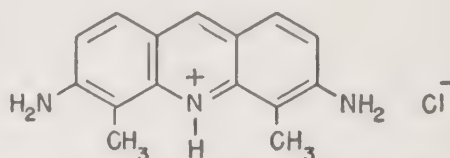


Acriflavine Hydrochloride, N.F. (3,6-Diamino-10-methylacridinium Chloride hydrochloride) is a reddish-brown, odorless, crystalline powder. It is soluble in water but nearly insoluble in ether, chloroform and liquid petrolatum. The solutions of the hydrochloride are acidic while those of acriflavine base are slightly basic. For some purposes, such as use on mucous surfaces,



solutions of the base appear to be less irritating than those of the salt.

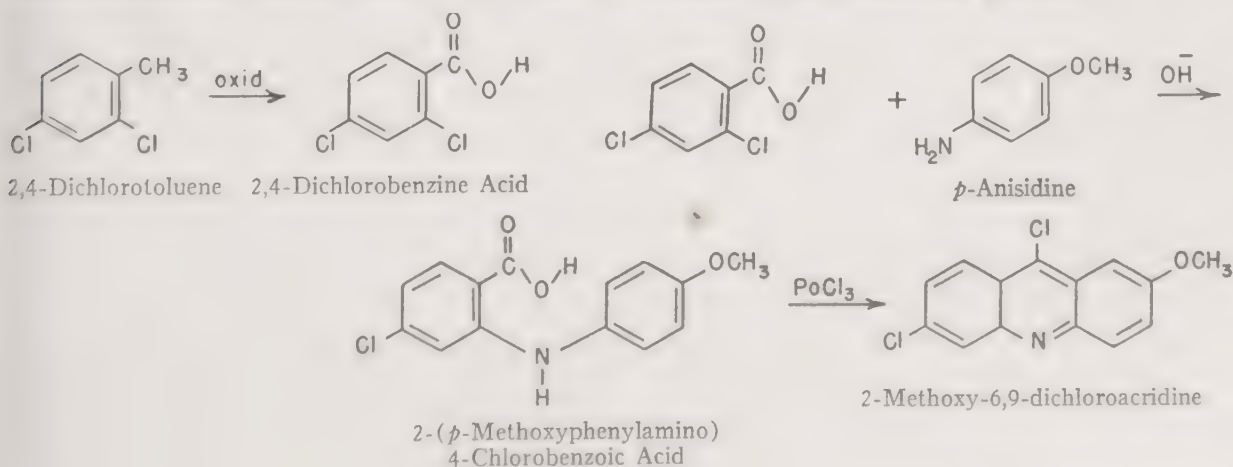
4,5-Dimethylproflavine Hydrochloride (3,6-Diamino-4,5-dimethylacridine hydrochloride, 1,9-Dimethylproflavine hydrochloride, 2,8-Diamino-1,9-dimethylacridine hydrochloride) is a brick-red powder, soluble in water, sparingly soluble in alcohol and practically insoluble in ether.



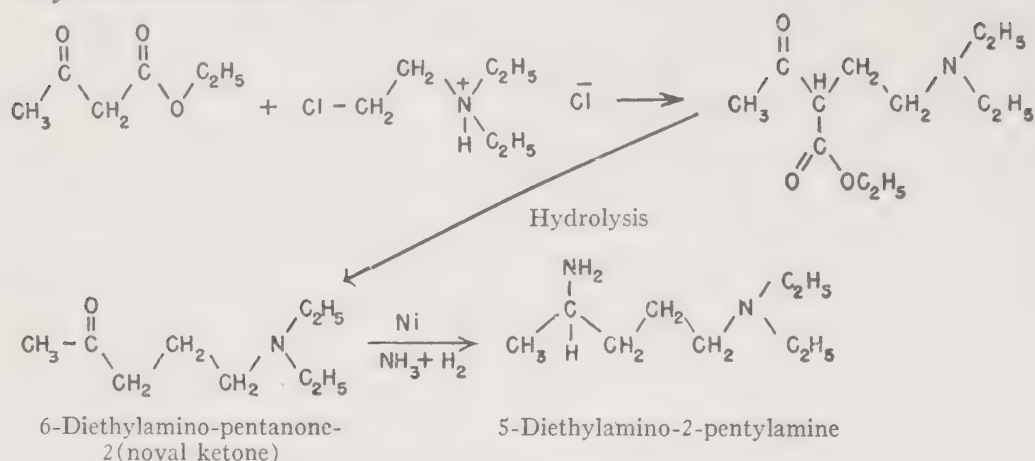
It is made from 2,6-diaminotoluene and anhydrous formic acid. The compound stains cloth and tissues. It has a high bacteriostatic index.

Quinacrine Hydrochloride (Mepacrine Hydrochloride) U.S.P. [Atabrine, Atebrin, 3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutyl-amino)-acridine dihydrochloride] is a yellow crystalline powder that has a bitter taste. It is soluble in alcohol and in water (1:35).

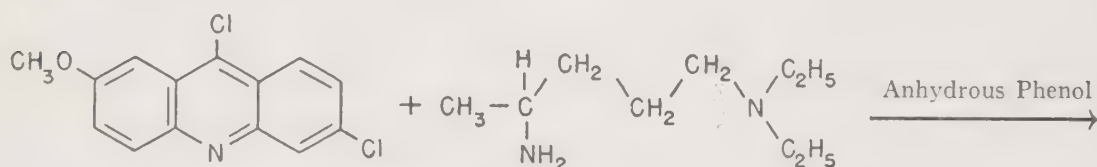
The acridine nucleus of quinacrine is synthesized in the following manner.



The amino side chain is synthesized from ethyl acetoacetate as follows.

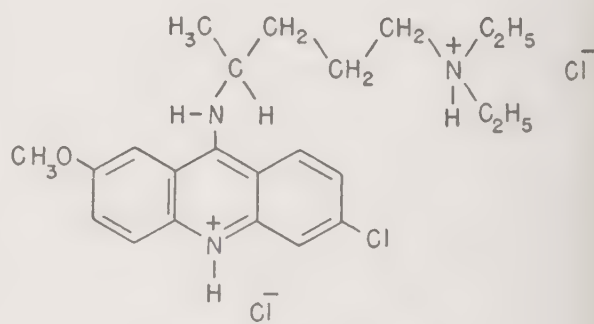


Quinacrine is obtained by condensing the 5-diethylamino-2-pentylamine with 2-methoxy-6,9-dichloroacridine in the presence of anhydrous phenol.



The water solution of quinacrine is fluorescent and has a pH of about 4.5. Like quinine, it is a schizontocidal agent and is well tolerated by man. It is as effective as quinine in the treatment of some types of malaria and is thought to be more effective for certain other types. During World War II, it was widely used in conjunction with pamaquine naphthoate since the two drugs are more effective when used in combination. The pamaquine naphthoate acts as a gametocidal agent and, therefore, is active on the malarial parasite at another stage of its development. Quinacrine can be employed during pregnancy or in the treatment of blackwater fever where the use of quinine is contraindicated. Another advantage over quinine is that it does not cause oral or visual disturbances. However, since it is a dye, it will color the urine and after extended use may turn the skin and eyeballs yellow. It is administered orally as tablets or capsules or may be given intravenously as a 1 per cent solution.

Hundreds of compounds have been studied



Quinacrine Hydrochloride

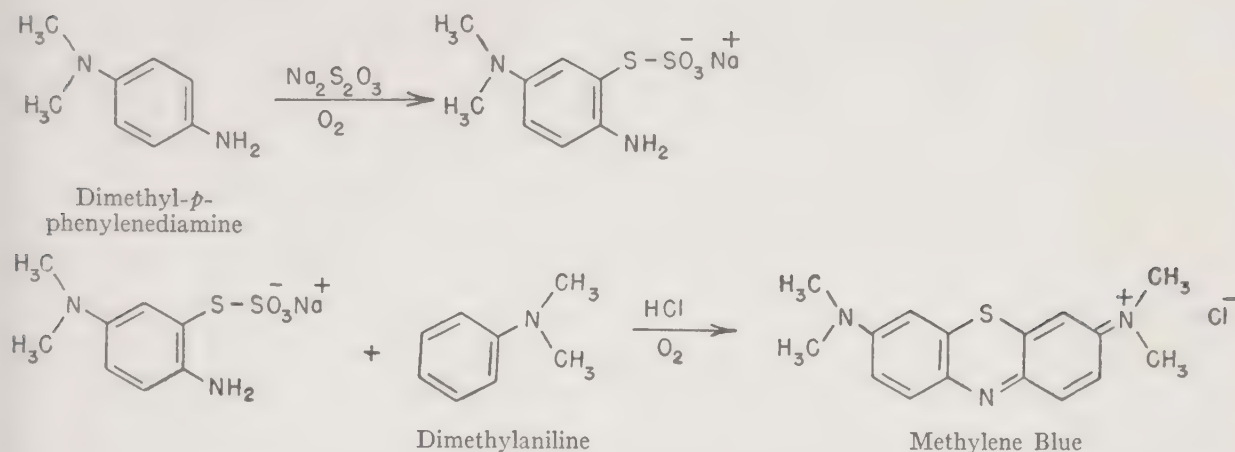
as antimalarial agents and some of these appear to be more effective than quinacrine. It is likely that quinacrine will be replaced by superior antimalarial agents.

The average dose is 0.1 Gm.

MISCELLANEOUS DYES

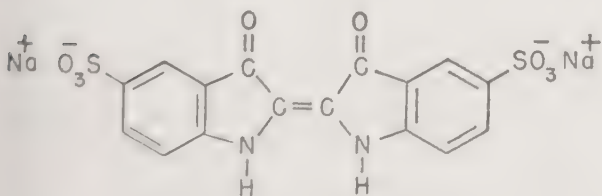
Methylene Blue U.S.P. (Methylthionine chloride) occurs as dark green crystals or powder with a bronze luster. It is soluble in chloroform, in water (1:25) and in alcohol (1:65). Its solutions may be sterilized by autoclaving.

Methylene blue may be synthesized as follows.



It has a comparatively low toxicity and is used to compare the renal function of the kidneys and also as a dye in vital nerve staining. It has some action against malaria but is inferior to the cinchona alkaloids, quinacrine and some of the new synthetics in this respect. It is a weak antiseptic that has been used in treating skin diseases and some urinary conditions. Methylene blue also is employed in the treatment of cyanosis resulting from the sulfonamide drugs and as an antidote for cyanide and nitrate poisoning. In proper concentrations, it has been shown to increase the rate of conversion of methemoglobin to hemoglobin. It is used to test for the presence of anaerobic bacteria in milk by the Thundberg technic.

Sodium Indigotindisulfonate N.F. (Indigo carmine) occurs as a blue powder or crystal with a copper luster. It is soluble in water (1:100), is slightly soluble in alcohol and almost insoluble in other organic sol-



Sodium Indigotindisulfonate

vents. It is affected by light, but its solutions may be sterilized by autoclaving.

It is used to determine renal function and to locate the ureteral orifices. It has been used to compare the action of the two kidneys. About 5 cc. of a 0.4 per cent solution is the usual dose given either intramuscularly or intravenously.

Dymixal N.N.R. is a mixture consisting of 46 per cent crystal violet, 31 per cent brilliant green and 23 per cent acriflavine. It is soluble in water, a 2.6 per cent aqueous solution being used for application to wounds. It is used in the "triple dye" treatment of burns and has the advantage that it forms a flexible eschar. The combination of dyes is effective against gram-positive and gram-negative organisms.

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21

Surface-Active Agents

ANIONIC AGENTS CATIONIC AGENTS

NONIONIC SURFACE-ACTIVE AGENTS

Surface-active agents represent a diverse group of chemical compounds which have the common property of modifying the characteristics of a boundary surface or interface between two liquids, a liquid and a solid or a liquid and a gas. Such modifying influence becomes manifest in the applicability of these compounds as detergents, wetting agents, foaming agents, dispersing agents, emulsifiers and related industrial and pharmaceutical agents. Overlapping performance of these agents is common. Soap acts as an emulsifier in ammonia liniment; it helps to subdivide the sesame oil into minute droplets enveloped by a continuous aqueous phase. Soap acts as a detergent and dispersing agent when it lifts dirt from the skin and promotes the separation of dirt particles from each other. Sodium lauryl sulfate acts as a foaming agent in bubble-bath powders and as a wetting agent in sulfur hair lotions by reducing the surface tension and permitting the powdered sulfur to sink below the liquid surface. Surface-active agents generally are used in low concentration and may prove effective in some instances at dilutions of 1:100,000.

Surface-active agents are characterized

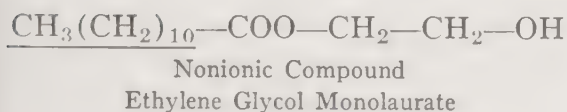
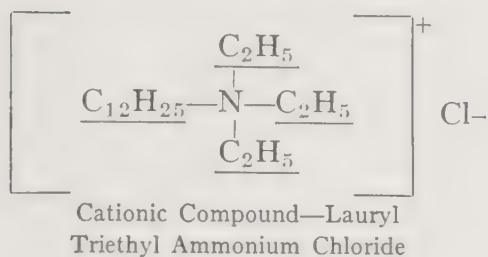
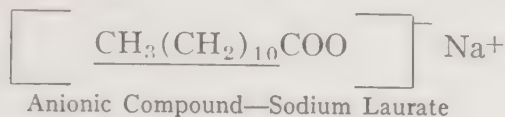
by the presence of hydrophilic or water solubilizing groups and lipophilic or fat solubilizing groups. Such groups as $-\text{OSO}_2\text{ONa}$, $-\text{COONa}$, $-\text{SO}_2\text{ONa}$, $-\text{OSO}_2\text{H}$ and $-\text{SO}_2\text{H}$ give strong hydrophilic properties to a compound, the sequence representing the approximate decreasing order of effectiveness. The following groups produce this effect to a lesser degree: $-\text{OH}$, $-\text{SH}$, $-\text{O}-$, $=\text{CO}$, $-\text{CHO}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$, $-\text{CN}$, $-\text{CNS}$, $-\text{COOH}$, $-\text{COOR}$, $-\text{OPO}_3\text{H}_2$, $-\text{OPO}_2\text{H}_2$, $-\text{OS}_2\text{O}_2\text{H}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$.

Lipophilic groups are typified by aliphatic hydrocarbon chains, aryl-alkyl groups and polycyclic hydrocarbon groups. The presence of unsaturated linkages such as $-\text{CH}=\text{CH}-$ and $-\text{C}\equiv\text{C}-$ helps promote stability in water and often locates the water solubilizing group.

Surface-active compounds are classified as anionic agents when the lipophilic group is present in that part of the molecule which acquires a negative charge upon ionization. They are classed as cationic agents when the lipophilic group is in the cation. A third class, nonionic surface-active agents, is characterized by the presence of weakly hydro-

philic groups and lipophilic groups in non-ionizable compounds, which render them water dispersible or water soluble.

The configuration of these classes may be represented by three examples:

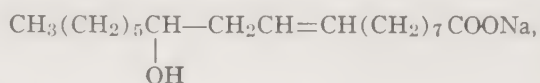


In each case, the underlined part of the molecule is lipophilic; the unmarked parts are hydrophilic.

Surface-active agents are colloidal electrolytes and thus are able to form ionic micelles. These tend to orient themselves with their long axes perpendicular to the interfacial boundary. At an oil-water interface, the hydrophilic group projects into the water layer and is referred to as a polar group. The lipophilic or nonpolar group projects into the oil layer. It is this phenomenon whereby the surface-active micelle is directed simultaneously into polar and nonpolar media which gives rise to such surface activity as dispersion, wetting, detergency and emulsification.

The mere presence of lipophilic and hydrophilic groups is not sufficient to render a compound surface active. There must be a balance between these groups. Thus, CH_3COONa , sodium acetate, is relatively too heavily weighted on the hydrophylic side and is very soluble in water but manifests no surface-active properties. As the hydrocarbon chain is lengthened to about ten carbon atoms, colloidal properties are exhibited, water and oil solubilities

of the respective hydrophilic and lipophilic groups are good and surface-active properties are displayed. Sodium laurate, $\text{CH}_3(\text{CH}_2)_{10}\text{COONa}$, is an example of a proper balance between lipophilic and hydrophilic groups. If the chain of carbons becomes too long, *viz.*, about 16, this influences the solubility in water of the polar group. Thus, sodium stearate, $\text{CH}_3(\text{CH}_2)_{16}\text{COONa}$, is insoluble in water and exhibits poor surface-active properties. It is too heavy on the lipophile side. If, however, a double bond is present near the middle of the carbon chain, as in sodium oleate, or if a hydrophilic group such as an OH is introduced in the lipophilic group, balance is restored. Sodium ricinoleate,



is water-soluble and is an excellent surface-active agent. The addition of too many double bonds or OH groups, while making the compound more water soluble, would again upset the balance, this time making it heavy on the hydrophile side, and surface-active properties would be markedly reduced or eliminated.

The large number of possibilities of introducing groups for the purpose of attaining a balance has given rise to the thousands of new compounds having surface active properties.

A selected number of typical examples of pharmaceutical interest will be described.

ANIONIC AGENTS

Sodium Lauryl Sulfate U.S.P. (Duponol) "is a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate [$\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OSO}_3\text{Na}$]."

This is prepared by sulfating long chain alcohols and neutralizing to form the sodium salts. The alcohols are derived by reduction of coconut oil and other fatty glycerides by high pressure hydrogenation with copper-chromium oxide catalyst or by sodium reduction.

It occurs as white or light-yellow crystals

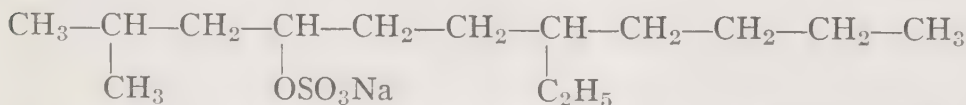
or flakes having a slight coconut fatty odor. It is soluble 1 in 10 parts of water. The official form permits up to 10 per cent of sodium sulfate.

Sodium lauryl sulfate is representative of the class of surface-active agents that accounts for about 20 per cent of the total production of these agents.

It is compatible with alkalis and with soaps, but unlike the latter, it is also unaffected by dilute acids, calcium or magnesium ions. An 0.1 per cent solution will exert detergent action in a hard water containing 2,500 p.p.m. of calcium. This makes it widely used in textile and other industrial applications. It is the basis of soapless shampoos, and serves as a unique tablet lubricant and as an emulsifier in preparing water miscible ointment bases.

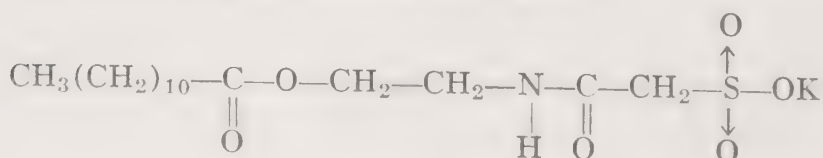
OFFICIAL OCCURRENCE	PER CENT SODIUM LAURYL SULFATE
U.S.P.	
Hydrophilic Ointment	1.0

Sodium Tetradecyl Sulfate (Sotradecol) is sodium 2-methyl-7-ethyl undecyl sulfate-4.



Sotradecol is a white, water-soluble powder made from synthetically prepared fatty acids and therefore claimed to be free of allergenic substances of natural origin. It is used in the form of 1 per cent, 3 per cent and 5 per cent aqueous solutions, buffered at pH 7.6, in the obliterative treatment of varicose veins. This highly branched chain type of alkyl sulfate appears to be a more effective vein obliterant than straight chain surface-active agents such as sodium morrhuate or sodium lauryl sulfate.

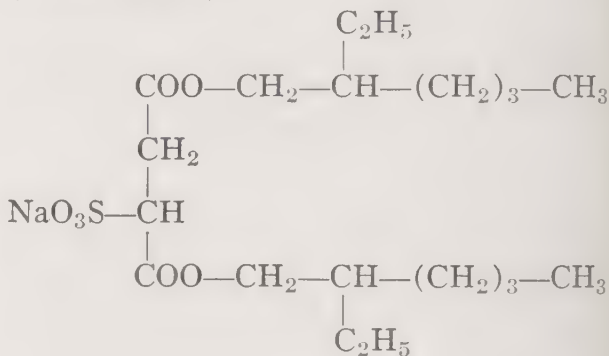
Sulfocolaurate A.D.R. is the lauric acid ester of the potassium salt of sulfoacetic acid amidified with β -amino ethyl alcohol.



It is prepared by esterifying the chloracetamide of β -amino ethyl alcohol with lauric acid and reacting the resulting product with potassium sulfite.

The commercial product contains 8 per cent potassium chloride. It is a white powder, sparingly soluble in cold water and very soluble at 37.5° C. It produces copious foam and is used in dentifrices as a foaming agent in concentrations of 1 to 2 per cent. It has been accepted for inclusion in Accepted Dental Remedies because of its lack of irritation to the tissues of the mouth in the concentration recommended.

Dioctyl Sodium Sulfosuccinate N.F. (Aerosol O.T.)



This is prepared by treating the reaction product of maleic anhydride and octyl alcohol with sodium bisulfite.

It is a white, waxlike, plastic solid, usually occurring in pellets, with an odor suggestive of octyl alcohol. It is soluble in alcohol, glycerin and petroleum benzin. It dissolves slowly, one part in seventy, in water. A 1 per cent solution has a pH of 6.5.

Of the several alkyl substituted sulfosuccinates designated as Aerosol products, the dioctyl is by far the most powerful wetting agent as determined by the Draves and

Clarkson test, which measures the sinking time of a skein of yarn under specified conditions.

By contrast with long chain sulfated alcohol type surface-active agents having terminal polar groups, Aerosol carries the polar groups in the middle of a branched chain. In the former type, the molecules at an oil-water interface can pack very closely together with their long axes parallel and perpendicular to the interface. A relatively large number will be required to cover a small surface area. In contrast, the molecules of Aerosol O.T., when oriented at the interface, are relatively short but considerably greater in area. A small number of molecules will be required to cover a given area. This illustrates the significance of molecular configuration of surface-active agents in comparing their relative efficiencies.

Aerosol O.T. is moderately stable in acid and mild alkali solutions; it is decomposed by strong bases. Its diverse uses include the wetting of wax molds to prevent bubbles in dental castings, the cleaning of fruits, the washing of laboratory and ampule glassware, the preparation of hydrophilic ointment bases, the solubilizing of cresol in water and the enhancement of bactericidal properties of antiseptics.

Hydroxystearin Sulfate, N.F. (Sulfated Hydrogenated Castor Oil, S.H.C.O.).

This is a mixture, rather than a chemical entity, of the anionic type. "Hydroxystearin Sulfate is a substance prepared by sulfating hydrogenated castor oil. When calculated on a moisture free basis, it contains not less than 8.5 per cent and not more than 9.5 per cent of organically combined sulfur trioxide (SO_3)."

The sulfated product is neutralized with alkali. The glycerin formed during processing is removed. Hydroxystearin sulfate is a sulfated soap of low iodine value, below 8, and relatively high acetyl value, 55 to 95. It is an amber ointmentlike mass, miscible with oils, glycerin and petrolatum and dispersible in water and alcohol. Its tackiness may be

overcome by admixture with 25 per cent petrolatum.

Combination of hydroxystearin sulfate with petrolatum, glyceryl or glycol monostearate and water, have been suggested as bases for hydrophilic ointments of the oil-in-water type emulsion compatible with a majority of official medicaments now prepared in lipophilic bases.

CATIONIC AGENTS

The most frequently used substances in this class are aliphatic quaternary ammonium salts and pyridinium salts, although arsonium, phosphonium and sulfonium salts and primary and secondary amine salts also exhibit properties common to cationic agents. Of the substituent hydrocarbon groups, one is usually a long chain of 8 to 16 carbon atoms, which may, however, be an interrupted chain modified by the inclusion of oxygenated and aryl groups. The other substituents may be short alkyl, aryl or aryl-short alkyl hydrocarbon groups.

Cationic agents, particularly quaternary ammonium and pyridinium salts, are unique in that they exhibit combined detergent and germicidal properties. They offer certain advantages over more common germicides such as phenols, iodine, dyes, mercurial and silver compounds in that they are more soluble in water, nonstaining, relatively less toxic or caustic, effective in high dilution and noncorrosive to metallic and rubber surgical appliances.

Some anionic agents have also proven germicidal, usually at low pH, but their action for the most part is limited to the inhibition of gram-positive organisms. Cationic agents inhibit both gram-positive and gram-negative bacteria and function best in neutral or alkaline media.

Cationic agents are believed to function by exhibiting a marked effect upon the metabolism of the bacterial organism. They are adsorbed upon the surface membranes of the bacteria and denature or disarrange the protein molecules. As a result of the

cytolytic damage, the cell contents seep out, a process which is analogous to hemolysis. The extent of such bacteriolysis has been correlated with germicidal efficacy.

Cationic agents are not, however, without disadvantages. They are incompatible with soap and other anionic agents. The large part of the quaternary ammonium salt molecule, being positively charged, combines with the large negatively charged part of the anionic agent. In high concentration, a precipitate or cloudiness is manifest. In low concentration, there is no visible manifestation of incompatibility, but bactericidal properties are reduced or completely lost.

In appraising the claims of germicidal efficacy appearing in the literature for the several available cationic germicides or comparing these with other germicidal agents, values obtained by standard F.D.A. phenol coefficient or agar plate *in vitro* tests must, to a large extent, be discounted. Many factors have been shown to vitiate the results or give erroneous values. Among these are the marked reduction in activity by the presence of serum and the bacteriostatic influence of traces of adsorbed cationic agent carried over on bacterial surfaces through several dilutions of culture media as a result of failure to provide effective inactivating agents. The naphthylamine sulfonic acids offer some promise as cationic inactivating agents.

In vivo tests would appear to give a more reliable index. The Nungester and Kempf technic, whereby a freshly segmented mouse tail is impregnated with a virulent bacterial organism, exposed for a predetermined time to the action of the germicide and introduced surgically into the peritoneal cavity of the animal, evaluates the germicide in terms of percentage survival of a number of test animals at different concentration levels of the germicide.

Another factor of importance is the toxicity of the germicide to body tissues. The Welch-Hunter toxicity test measures the ratio of the dilution volume tolerated by tissue (as for example phagocytes) to the

dilution volume that is germicidal. A ratio of more than one would obviously indicate unfitness for use. Many germicides in use today have indices above one.

Until results which utilize these more rational technics are published, it is pointless to give numerical data representative of germicidal concentrations.

Benzalkonium Chloride U.S.P. (Zephiran, Roccal) also is called alkyldimethylbenzylammonium chloride.

"Benzalkonium Chloride is a mixture of alkyl dimethyl-benzyl ammonium chlorides of the general formula $C_6H_5CH_2N(CH_3)_2RCl$, in which R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$."

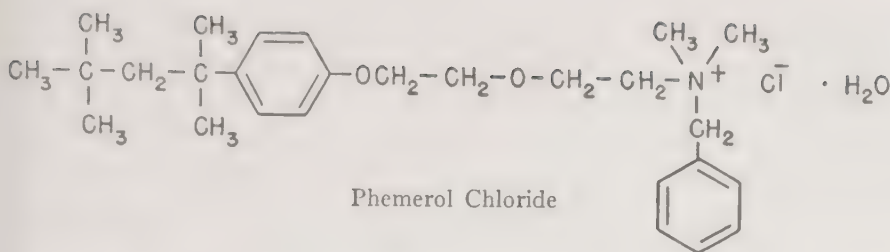
It is a white, amorphous, bitter-tasting powder, slightly soluble in benzene and very soluble in water. Aqueous solutions are colorless, alkaline to litmus and foam strongly.

Benzalkonium Chloride possesses wetting, detergent, keratolytic and emulsifying actions. It is used as a surface antiseptic for intact skin and mucosa at 1:1,000 to 1:10,000 concentration. Above 1:1,000 it proves irritant on prolonged contact. It is effective for many pathogenic nonsporulating bacteria and fungi after several minutes exposure. For irrigation, 1:20,000 to 1:40,000 solutions are employed. For sterile storage of surgical instruments, 1:1,000 solutions are used, 0.5 per cent of sodium nitrite being added as an anticorrosive agent.

For presurgical antisepsis, all traces of soap used in preliminary scrubbing must be removed, or inactivation of the cationic detergent will ensue. When tinted solutions are used to help delineate area of operation, cationic type dyes must, in general, be selected to avoid incompatibility.

Phemerol Chloride N.N.R. is [*p*-(2-methyl-4,4-dimethyl pentane-2) (phenoxyethoxy-ethyl)] -dimethylbenzyl ammonium chloride monohydrate.

This compound differs from Benzalkonium Chloride in that the long alkyl group has been replaced by a group bearing

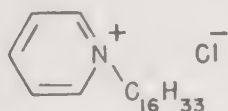


phenyl and ether linkages between the terminal alkyl group and the quaternary nitrogen atom. Many such derivatives have been synthesized for the purpose of enlarging the spectrum of bacterial effectiveness.

Phemerol Chloride is a colorless, odorless, bitter, crystalline powder, soluble in water and slightly soluble in chloroform. A 1 per cent solution has a pH of 5. Solutions above 2 per cent are precipitated by mineral acids and many salts.

Its actions and uses are similar to those of Benzalkonium Chloride, being employed at 1:1,000 concentration for general antiseptics. For irrigation of the eye, nose or mucous membranes, a 1:5,000 solution is employed. An alcoholic tincture (1:5,000) is also available.

Cetyl Pyridinium Chloride (Ceepryn).



Cetyl Pyridinium Chloride

In this compound the quaternary nitrogen is part of a heterocyclic nucleus. The cetyl derivative has been selected in preference to other alkyl derivatives studied because of its maximum bactericidal activity. It is also believed that the absence of a benzyl group reduces the toxicity of the compound.

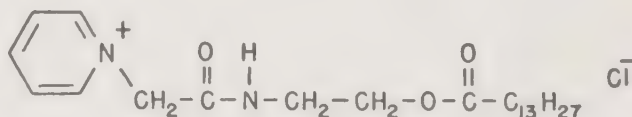
Cetyl pyridinium chloride is a white powder, freely soluble in water and alcohol.

It is compatible with ephedrine hydrochloride, procaine hydrochloride, urea and allantoin. It is incompatible with tannic acid, picric acid, alum and soap.

It has proven germicidally effective over a pH range of 5 to 10. It is available for use

as a general antiseptic in 1:1,000 aqueous solution and in tinted tinctures from 1:200 to 1:1,000 concentration; it also is available in the form of jelly, powder, suppository and as a 1:4,000 phosphate-buffered gargle.

Emulsol 607 is the myristic acid ester of colamine formylmethyl pyridinium chloride.



In a long series of compounds studied, this complex long chain derivative of pyridinium chloride, with a terminal myristate (or alternatively, laurate) grouping, proved the most effective bactericidally. It is illustrative of a careful balance between lipophilic and hydrophilic groups.

It is a white or tan, flaky, odorless powder, very soluble in water, alcohol and acetone, and has the general properties of the class of cationic agents. Because of a low toxicity index, about 0.6, and relatively high bactericidal and fungicidal activity, it has been advocated for such diversified uses as sanitary laundering of textiles and dish washing, general disinfection, cosmetic preservation, presurgical and other topical antiseptics and in fungus infections. In connection with these uses, possible inactivation by trace anionic agents encountered must be given consideration.

It is used in concentrations of 1:1,000 to 1:30,000.

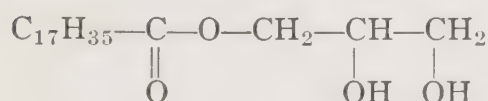
Trimethyl Cetyl Ammonium Pentachlorophenate (Hyamine 3258, T.C.A.P.) is $C_{16}H_{33}(CH_3)_3NOC_6Cl_5$. This compound is available commercially as a tan-colored, 40 per cent paste in water. It is miscible with warm water, yielding a dispersion which is

at maximum stability between pH 6 and 7.5. At concentrations above 5 per cent, gelling occurs. In one per cent solutions in 20 per cent alcohol it is an excellent mildew-proofing agent for containers, textiles and leather. It is bactericidal and fungicidal and has been used in athlete's foot preparations in 0.5 to 2 per cent concentrations.

NONIONIC SURFACE-ACTIVE AGENTS

In this class of agents the hydrophilic character is usually obtained from the presence of free hydroxyl or ether oxygen groups, the lipophilic character from fatty acid hydrocarbon chains of C_{10} to C_{18} .

Glyceryl Monostearate N.F. (Monostearin).



"Glyceryl Monostearate occurs as a white wax-like solid or as white wax-like beads or flakes. It has a slight agreeable fatty odor and taste. It is affected by light."

It melts at $57^{\circ}C$. and is soluble in fat, alcohol, most organic solvents, fixed oil, and mineral oil. It is insoluble in water, but is readily dispersible in hot water with the aid of an anionic or cationic agent.

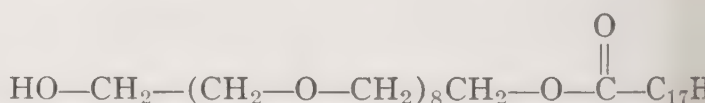
Glyceryl Monostearate is an example of the nondispersible type of nonionic agent. Many compounds of this type are available; the mono-oleates, monopalmitates, monolaurates and monostearates of ethylene, diethylene and propylene glycols, glycerol and sorbitol are most frequently used. Though fatty or oily in appearance, their free hydroxyl groups cause them to lower the surface tension of the oils in which they may be dissolved. They also act as mutual solvents for polar and nonpolar compounds. They may form water-in-oil or oil-in-water emulsions.

These unique properties give rise to such applications as emulsion stabilizers, dispersing agents of pigments in oils or food solids in fats such as cocoa in chocolate fat, short-

ening improvers to prevent leakage of milk from margarine, solvents for the difficultly dispersible phospholipids such as lecithin and blenders of soap with mineral oil or kerosene. A few, such as propylene glycol monostearate, have been used to prepare hydrophilic suppository bases.

Polyethylene Glycol 400 Monostearate (Nonaethylene Glycol Monostearate).

This is a soft, white, waxy solid, m.p. 26° , soluble in many organic solvents and dispersible in hot water. The latter property characterizes a number of nonionic agents that contain a limited number of ether linkages in the hydrophilic part of the molecule. Other compounds in this water-dispersible group include polyglycerol and sorbitan fatty esters.

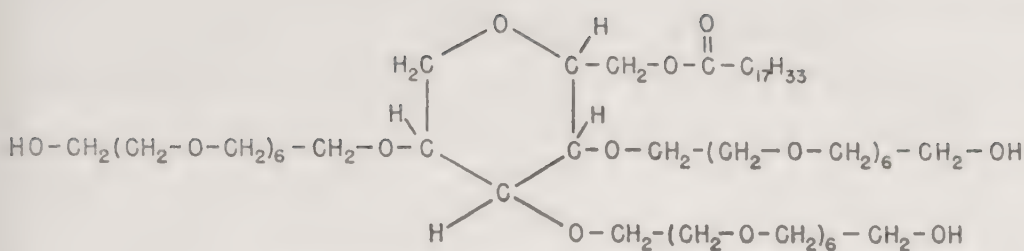


These agents, when dispersed in water, act as thickeners in place of vegetable gums and as self-dispersible lubricants. They form water-in-oil as well as oil-in-water type emulsions. They are used in preparing "soluble oils," clear oily products containing such substances as cresols, kerosene, or perfume oils, which form emulsions directly upon addition to water.

Polyoxyethylene Sorbitan Mono-oleate (Tween 80).

This compound differs from the other two examples in that it is completely soluble in water as well as in many fixed oils and organic solvents. The several chains of ether linkages terminating in free hydroxyl groups account for the water solubility. The hydrophilic groups slightly overbalance the lipophilic oleate group. It is not as soluble in some oils as the water-dispersible type of nonionic agent; for example, it is insoluble in mineral oil. Frequently, combinations of water-dispersible, nondispersible and water-soluble nonionic agents are used to produce more stable emulsions.

The therapeutic agent Sorlate consists of 0.5 Gm. capsules of Tween 80. It is used in



SELECTED READING

- treating malnutrition due to faulty fat absorption in dosages of 6 grams daily.
- Water-soluble nonionic agents are especially useful in the presence of high electrolyte concentration. They also have the unique property of dispersing perfume oils or oil-soluble vitamins in water, producing clear solutions.
- Other compounds in this water-soluble class having similar characteristics are certain partial fatty acid esters of highly polymerized glycerol and of long chain polyoxyethylene, polyoxypropylene and methoxy polyoxyethylene glycols.
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22

Terpenes and Related Compounds

TERPENE HYDROCARBONS

ACYCLIC

MONOCYCLIC

DICYCLIC

TERPENE ALCOHOLS

TERPENE ETHERS

TERPENE ALDEHYDES

TERPENE KETONES

Terpenes are hydrocarbons having the empirical formula $C_{10}H_{16}$ or $(C_5H_8)_2$. Actually, the term "terpenes" is used to designate compounds composed of from one to six isoprene units (C_5H_8) or polymers of this unit, such as rubber. A classification of the terpenes is given in Table 30.

Oxygenated derivatives of these terpene hydrocarbons are known as camphors, and they include alcohols, ethers, aldehydes and ketones. Camphors are usually the more important constituent, or constituents, of the volatile oils. A few have medicinal value but most of them are used in flavoring or perfumery. They are the primary constituent in terpeneless volatile oils because in these oils practically all of the terpene hydrocarbons have been removed. The value of terpeneless volatile oils is that the camphors are more soluble in water and alcohol, thus are more suited for flavoring and perfumery.

The principal source of terpenes and camphors are the volatile oils derived from over 87 plant families, especially *Rutaceae* and *Coniferae*. For the most part, these oils contain hydrocarbons of the general formula

$(C_5H_8)_n$ or derivatives of these substances. In Table 31 are found some volatile oils which are used because of constituents that are neither terpenes nor camphors. It has been found that the terpene hydrocarbons

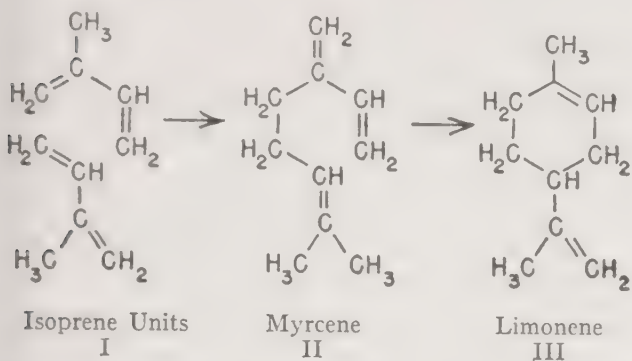
TABLE 30. CLASSIFICATION OF TERPENES

CLASS	EMPIRICAL FORMULA	EXAMPLE	ISOPRENE UNITS
Hemiterpenes ...	C_5H_8	Isoprene	1
Terpenes			
Olefinic	$C_{10}H_{16}$	Myrcene	2
Monocyclic ...	$C_{10}H_{16}$	Limonene	2
Bicyclic	$C_{10}H_{16}$	<i>d</i> -Pinene	2
Sesquiterpenes ..	$C_{15}H_{24}$	Santalene	3
Diterpenes	$C_{20}H_{32}$		4
Triterpenes	$C_{30}H_{48}$		6
Polyterpenes	$(C_5H_8)_n$	Rubber	<i>n</i>

are made up of two or more isoprene units; this discovery has led to the development of the "isoprene rule" in connection with the chemistry of some natural products (Vitamin A).

Terpene formation in plants is not well understood, but it can be imagined that two or more isoprene or oxygenated isoprene molecules condense to form acyclic, mono-

cyclic or dicyclic structures. Oxidation and reduction processes then give rise to camphors.



The above diagram does not represent an equation for the formation of II or III, but serves to illustrate the relationship of terpenes. In terpenes, the double bonds are very

TERPENE HYDROCARBONS

ACYCLIC ($C_{10}H_{16}$)

Acyclic terpene hydrocarbons represent a minor group of volatile oils used in pharmacy. Myrcene, found in Oil of Myrcia, is the best example.

MONOCYCLIC ($C_{10}H_{16}$)

There are a number of monocyclic terpene hydrocarbons, but only two are found with any regularity in the official volatile oils:

Limonene is found in a dextro and levo form, as well as in a racemic form known as dipentene. It is found in oils of bitter orange, lemon, orange (95 per cent) and spearmint. In these oils, it is the main terpene con-

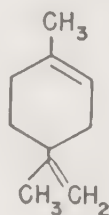


TABLE 31. VOLATILE OILS CONTAINING VALUABLE NON-TERPENE COMPOUNDS

OIL OF	COMPOUND	USES
Anise U.S.P.	Anethole 80-90%	Carminative and flavor
Cinnamon U.S.P.	Cinnamic aldehyde 80%	Carminative and flavor
	Eugenol	
Clove U.S.P.	Eugenol n.l.t. 82%	Counterirritant, flavor, mild anesthetic
	Benzyl alcohol	
Gaultheria U.S.P.	Methyl salicylate n.l.t. 98%	See Chapter 15
Fennel U.S.P.	Anethole	Carminative
Myristica U.S.P.	Eugenol and Cymene	Carminative and flavor
Orange U.S.P.	Methyl anthranilate	Flavor
Rose U.S.P.	β -Phenylethyl alcohol	Perfume
Sassafras U.S.P.	Safrol 80%	Flavor and disinfectant
Birch Tar, Rectified N.F.	Methyl salicylate, phenols, acids	Local stimulant and antiseptic
Bitter Almond N.F.	Benzaldehyde 95%, HCN 3%	Flavor
Mustard N.F.	Allyl isothiocyanate	Irritant and vesicant
Myrcia N.F.	Eugenol n.l.t. 50%	Perfume
Pimenta N.F.	Eugenol	Carminative and flavor
Orange Flowers N.F.	Methyl anthranilate	Perfume and flavor
Thyme N.F.	Thymol 20-30%, Carvacrol	Antiseptic, perfumes

prone to rearrangement; thus, several different compounds are possible in each classification.

In general, the terpene hydrocarbons are insoluble in water and soluble in organic solvents, including fixed and volatile oils. All $C_{10}H_{16}$ compounds, except camphene, are volatile liquids, lighter than water and permitting of vacuum or steam distillation without decomposition.

stituent. It is comparatively stable, but will oxidize on exposure to air. In Orange Oil U.S.P., a terebinthinate odor is thus produced, making the oil unsuitable for dispensing (U.S.P. p. 365).

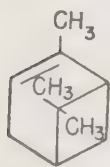
Phellandrene is found in alpha and beta forms in oils of fennel, cinnamon, pimenta and star anise. Phellandrene is quite unstable, easily decomposed by heat and readily oxidized.

TABLE 32. TERPENE HYDROCARBONS FOUND IN OFFICIAL VOLATILE OILS

HYDROCARBON NAME	FORMULA	OIL OF
ACYCLIC		
Myrcene	$C_{10}H_{16}$	Myrcia
MONOCYCLIC		
Limonene	$C_{10}H_{16}$	Spearmint, turpentine, lemon, orange, caraway
Phellandrene	$C_{10}H_{16}$	Pimenta
DICYCLIC		
α -Pinene	$C_{10}H_{16}$	Turpentine, coriander, juniper, eucalyptus, sassafras, thyme
Camphene	$C_{10}H_{16}$	Juniper, thyme, turpentine
Carene	$C_{10}H_{16}$	Pine needles
SESQUITERPENE		
ACYCLIC		
None		
CYCLIC		
Cadinene α & β	$C_{15}H_{24}$	Cubebs, juniper, pine needle
DICYCLIC		
None		
TRICYCLIC		
Cedrene	$C_{15}H_{24}$	Cedar

DICYCLIC

α -Pinene is very widely distributed in nature where it occurs primarily in *Coniferae* (See Table 32). It is one of the few terpenes that can be obtained in a relatively pure state. There are two asymmetric carbon atoms, thus providing four optically active and two racemic forms. The main source of α -pinene is Turpentine Oil U.S.P.



α -Pinene is a mobile, colorless liquid. Like most terpenes, it will undergo autoxidation by contact with oxygen of the air; thereafter, it becomes partially resinified. Old turpentine oils develop oxygenated compounds such as oxides, peroxides and alcohols.

The chemical reactivity of α -pinene makes it readily converted into other terpenes and oxygenated terpenes. It serves as a starting material for the synthesis of camphor and terpin hydrate (q.v.).

A product of turpentine oil called terebene is prepared by treating the oil with sulfuric acid, allowing the mixture to stand

for 12 to 18 hours, washing with an aqueous sodium carbonate solution, drying and distilling. Terebene is a mixture of hydrocarbons, composed in part of camphene, dipentene, terpinene and cymene; no pinene is present. It has been employed in the treatment of many illnesses, but its true value is questionable. The pharmacologic properties of terebene are very similar to those of turpentine.

TERPENE ALCOHOLS

Terpene alcohols are frequently found, either free or in ester combination, in volatile oils. They contribute in large measures to the odor and perfume value of oils. Two, menthol and santalol, are used as medicinal agents.

Linalool is present free and as the acetate ester in Bergamot Oil N.F. (n.l.t. 36 per cent), Bitter Orange Oil N.F., Coriander Oil U.S.P. and Lavender Oil U.S.P. (n.l.t. 30 per cent). It is a tertiary alcohol having two double bonds. Thus, it is difficult to esterify and reacts characteristically with reagents that add to double bonds.

TABLE 33. TERPENE ALCOHOLS FOUND IN OFFICIAL VOLATILE OILS

ALCOHOL NAME	FORMULA	OIL OF
ACYCLIC		
Linalool	$C_{10}H_{18}O$	Myrcia, thyme, lavender, rose, bergamot, coriander, orange
Geraniol	$C_{10}H_{18}O$	Rose, geranium,* lavender, citronella*
Citronellol*	$C_{10}H_{18}O$	Citronella, geranium
MONOCYCLIC		
Menthol	$C_{10}H_{20}O$	Peppermint
Terpin Hydrate	$C_{10}H_{20}O_2 \cdot H_2O$	Synthetic
DICYCLIC		
Borneol	$C_{10}H_{18}O$	Lavender, rosemary
Thujyl	$C_{10}H_{18}O$	Wormwood
SESQUITERPENE		
ACYCLIC		
Farnesol	$C_{15}H_{26}O$	Citronella,* rose, veroli*
CYCLIC		
Santalol	$C_{15}H_{24}O$	Sandalwood
TRICYCLIC		
Cedrol	$C_{15}H_{26}O$	Cedar

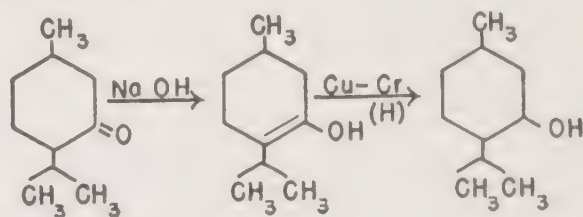
* Not an official volatile oil.

Menthol U.S.P. is a terpene secondary alcohol containing three asymmetric carbon atoms. This structure allows the formation of eight stereoisomeric menthols, of which four, *d*- and *l*-menthol and *d*- and *l*-neomenthol, are known. It has been a medicament for many years, and occurs primarily in peppermint oils, as free *l*-menthol (see formula) and, to a lesser extent, as menthyl acetate. The alcohol may be prepared synthetically by the reduction of thymol and the resolution of the racemate to obtain the *l* or *d* form. The U.S.P. recognizes the two optically active forms and the racemic form.

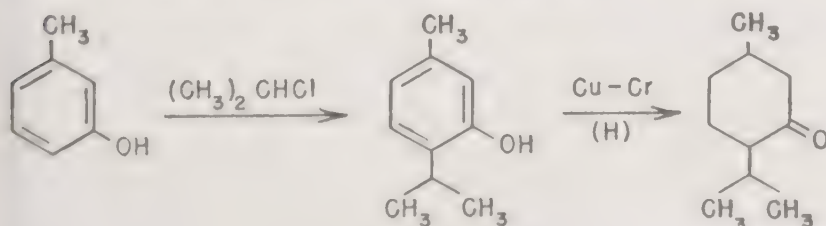
A synthetic process in present use starts with *m*-cresol and, in the difficult step of

reduction, uses copper chromite as the catalyst.¹

The ketones, a mixture of menthone and isomenthone, are treated with sodium hydroxide to convert them to the enol form. By reduction of the enol form, racemic menthol is obtained.



The mixture of isomeric menthols for most purposes presents no difficulty and are equally as useable as natural *l*-menthol or the pure synthetic *dl*-menthol. In toxicity



and pharmacologic properties, the difference is, however, that all the stereoisomers except *dl*-menthol have a disagreeable odor and an unpleasant taste.

Menthol usually occurs as needlelike crystals or in fused masses. It has a sharp, peppermintlike odor, is only slightly soluble in water, but is soluble in organic solvents or in fixed and volatile oils. Eutectic mixtures are formed with a number of substances such as camphor, phenol, chloral hydrate and thymol.

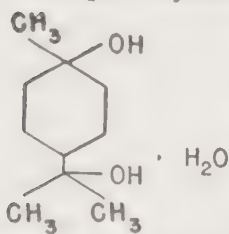
Menthol is used² primarily in external preparations or in sprays and solutions designed for use in the nasal passages or mouth. A decided cooling effect is noticed on application to the skin and a slight anesthetic action accompanies this. It also possesses some antiseptic action, as well as the action of a counterirritant. These combined properties make menthol a useful ingredient in lotions, nasal preparations, vapors for breathing, analgesic balms, cough drops, etc. Internally, the value of menthol is questionable, but it is used for nausea and dyspepsia.

OFFICIAL OCCURRENCE	PER CENT MENTHOL
N.F.	
N.F. Antiseptic Solution.....	0.05
Compound Menthol Ointment	10.0
Compound Menthol Spray...	1.0
Aromatic Spray	0.2
Compound Ephedrine Spray.	1.0
Compound Zinc Sulfate Powder	0.1

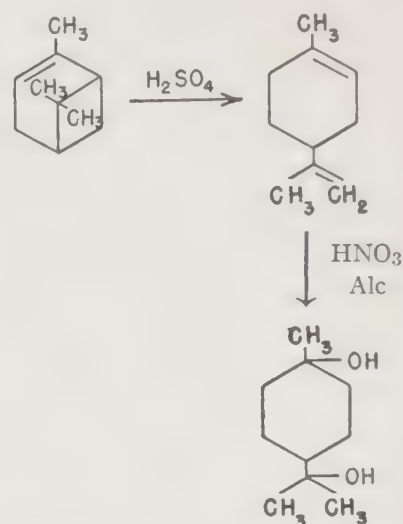
Menthyval is the valeric acid ester of menthol. It is a liquid which is said to possess mild sedative properties for use in anxiety states, hysteria and in motion sickness.

The average dose is 4 to 8 drops.

Terpin Hydrate N.F. (1:8 Terpin) is a dihydroxy terpene alcohol that may be present in some fresh volatile oils and is developed in some oils on standing. It is prepared commercially by treating turpentine oil with sulfuric acid,



nitric acid and alcohol, and allowing the mixture to stand several days.



The α -pinene is the constituent which is converted to terpin hydrate. By acid treatment, dipentene, geraniol and linalool also produce terpin hydrate. The removal of a mole of water from terpin hydrate forms the anhydride known as cineole or eucalyptol (q.v.). Phosphoric acid treatment may remove a mole of water at four different positions, and this gives rise to a group of terpeneols that are valuable in perfumery because of their lilac odor.

Terpin Hydrate exists usually as colorless crystals or as a white powder that is slightly soluble in water (1:200), soluble in alcohol (1:13) or slightly soluble in organic solvents.

It has been used for many years as an expectorant in cough preparations, although there is little scientific evidence of its value.

The average dose is 68 mg.

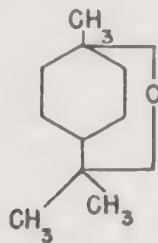
OFFICIAL OCCURRENCE	PER CENT TERPIN HYDRATE
N.F.	
Terpin Hydrate Elixir.....	1.7
Terpin Hydrate and Codeine Elixir	1.7

Santalol (C₁₅H₂₄O) is a sesquiterpene alcohol that is found as the principle constituent in East Indian sandalwood oil. There are two forms, alpha and beta; the former is tricyclic and the latter is dicyclic. It is used with salicylic acid in the compound

santyl (q.v.) and in the oil as a urinary antiseptic for gonorrheal urethritis. Its usefulness as a urinary antiseptic is very doubtful.

TERPENE ETHERS

Eucalyptol (Cineol) U.S.P. (Cajuputol, Cineole 1:8) is a terpene inner ether found in oil of eucalyptus and other oils (See Table 34). It may be obtained synthetically by the dehydration of terpin hydrate.



Eucalyptol

Eucalyptol is a clear liquid with a characteristic odor; it is insoluble in water but soluble in oils or organic solvents.

It has been administered internally, but such use is unsound. Primarily, it is used as a flavor and as an antiseptic in mouth washes, nasal sprays and throat preparations.

OFFICIAL OCCURRENCE N.F.	PER CENT EUCALYPTOL
N.F. Antiseptic Solution.....	0.01
Alkaline Aromatic Solution.....	0.1
Aromatic Spray	0.2
Compound Menthol Spray.....	0.2
Compound Zinc Sulphate Powder	0.1

TABLE 34. TERPENE ETHERS AND PEROXIDES FOUND IN OFFICIAL VOLATILE OILS

ETHER NAME	FORMULA	OIL
ETHER		
1:8 Cineole	$C_{10}H_{18}O$	Eucalyptus, cajuput, wormseed, cardamom, spearmint, lavender
PEROXIDE		
Ascaridole	$C_{10}H_{16}O_2$	Chenopodium

TABLE 35. TERPENE ALDEHYDES FOUND IN OFFICIAL VOLATILE OILS

ALDEHYDE NAME	FORMULA	OIL
ACYCLIC		
Citral	$C_{10}H_{16}O$	Lemon grass, rose
Citronellal	$C_{10}H_{18}O$	Citronella*

* Not an official volatile oil.

Ascaridole is the principal ingredient of chenopodium oil (45 to 70 per cent). It is an unsaturated terpene peroxide that will decompose in a violent explosion when exposed to heat and acid.

Usually it is not isolated, but is used in chenopodium oil as an anthelmintic for hookworm, roundworm and ascarides (from which comes its name). Due to its irritant and toxic properties, the oil is seldom used.

TERPENE ALDEHYDES

Citral occurs primarily in oil of lemon grass (about 80 per cent) and in oil of lemon (8 per cent). It exists in two geometric forms, α and β . It is an aliphatic aldehyde containing two double bonds. Terpeneless lemon oil is nearly pure citral, α and β , and is more soluble in water than in the natural oil, about sixteen times the flavoring ability and does not develop a terebinthinate odor. It is in a great measure responsible for the lemon odor.

TERPENE KETONES

Camphor U.S.P. is a terpene ketone and may be obtained from the wood of *Cinnamomum camphora* by distillation or produced synthetically using α -pinene isolated from turpentine oil.

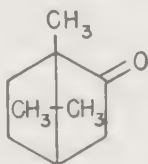


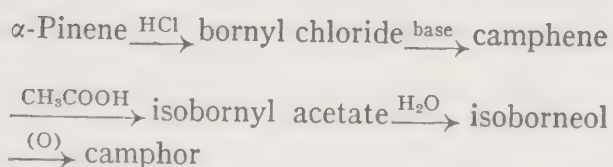
TABLE 36. TERPENE KETONES FOUND IN OFFICIAL VOLATILE OILS

KETONE NAME	FORMULA	OIL
MONOCYCLIC		
Menthone	$C_{10}H_{18}O$	Peppermint, geranium,* pennyroyal*
Carvone	$C_{10}H_{14}O$	Caraway, dill,* spearmint
DICYCLIC		
Camphor	$C_{10}H_{16}O$	Wood of <i>Cinnamomum Camphora</i> Ness. and synthetic, rosemary, sassafras
Thujone	$C_{10}H_{16}O$	Cedar, thuja, sage,* tansy,* wormwood

* Not an official volatile oil.

TABLE 37. OFFICIAL VOLATILE OILS CONTAINING A TERPENE OR A CAMPHOR AS A MAIN CONSTITUENT

VOLATILE OIL	TERPENE AND CAMPHOR	USES
Cedar Leaf U.S.P.	Cedrene, cedrol, thujone	Perfume
Coriander U.S.P.	Pinene, cineole, linalyl acetate	Carminative, flavor
Eucalyptus U.S.P.	Pinene, cineole n.l.t. 70%	Flavor, antiseptic, perfume
Fennel U.S.P.	Fenchone, pinene	Carminative
Lavender U.S.P.	Linalyl acetate, geraniol, cineole	Perfume, flavor
Lemon U.S.P.	Pinene, geraniol, citral	Flavor
Myristica U.S.P.	Pinene, geraniol	Carminative, flavor
Orange U.S.P.	Limonene (95%), linalool	Flavor
Peppermint U.S.P.	Menthol n.l.t. 50%, menthyl acetate, menthone	Flavor, carminative
Rose U.S.P.	Geraniol, nerol, citral	Perfume
Rosemary U.S.P.	Bornyl acetate, borneol, cineole, camphor	Carminative, flavor
Sassafras U.S.P.	Pinene, camphor	Flavor, disinfectant
Spearmint U.S.P.	Carvone, cineole, limonene	Carminative, flavor
Turpentine U.S.P.	Pinene, camphene, dipentene	Solvent, counterirritant
Turpentine, Rectified U.S.P.	Pinene, camphene, dipentene	Antiseptic, counterirritant
Bergamot N.F.	Linalyl acetate, linalool	Perfume
Bitter Orange N.F.	Limonene, linalyl acetate	Flavor
Caraway N.F.	α -Carvone, limonene	Carminative
Cardamom N.F.	Cineole	Flavor
Chenopodium N.F.	Ascaridole	Anthelmintic
Juniper N.F.	Pinene, cadinene, camphene	Flavor, irritant, carminative
Myrcia N.F.	Linalool, myrcene	Perfume
Pimenta N.F.	Cineole, phellandrene	Flavor, carminative
Pine Needles N.F.	Bornyl acetate, pinene, carene, cadinene	Flavor, antiseptic
Thyme N.F.	Pinene, linalool, camphene	Perfume, antiseptic



The camphor structure has two asymmetric carbon atoms, but due to the strain on the connecting bonds, only two optically active forms have been prepared.

Natural camphor is the dextro form and synthetic camphor is a racemic form, but for industrial or medicinal use the difference

is insignificant. Actually, the greater activity of the levo forms makes synthetic camphor more powerful physiologically than natural camphor.

Usually, camphor is supplied as white crystalline masses or as white, translucent, small cakes. It has a characteristic odor and a sharp, burning taste. Powder camphor is readily prepared by rubbing camphor with a small quantity of alcohol, ether or chloroform. It is slightly soluble in water (1:800) and soluble in alcohol or organic solvents. A eutectic mixture is formed with menthol,

thymol, chloral hydrate, salol, phenol or resorcinol.

Camphor is most commonly employed locally as a mild antiseptic, analgesic and antipruritic (see official occurrence). The sensation of coolness it creates when applied either to the epidermis or to the nasal passages makes it a pleasant medicinal agent. In paregoric and in cold preparations it is used because there is thought to be a slight expectorant and diaphoretic action. Its use internally as a circulatory and respiratory stimulant is unsound.

The application of the many camphor preparations allows it to gain entrance into the system, where it is reduced to the alcohol, camphorol, and then combines with glycuronic acid by a glucosidic linkage and is excreted in the urine.

The average dose is 0.2 Gm.

OFFICIAL OCCURRENCE	PER CENT CAMPHOR
U.S.P.	
Camphor and Soap Liniment.	4.5
Camphor Liniment	20.0
Camphor Water	0.2
Flexible Collodion	2.0
Camphorated Opium Tincture	0.4
Chloroform Liniment	1.35

N.F.

Camphor Spirit	10.0
Camphor Ampuls	...
Camphor Ointment	22.0
Lead Subacetate Cerate.....	2.0
Belladonna Liniment	5.0
Solid Soap Liniment.....	2.5
Aromatic Spray	0.2
Compound Menthol Spray....	1.0
Camphorated Phenol	60.0
Aconite and Chloroform	
Liniment	...
Compound Opium and	
Glycyrrhiza Mixture	...

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23

Carbohydrates or Saccharides

Carbohydrates are synthesized by chlorophyll-containing plants from carbon dioxide and water in the presence of sunlight. The first carbohydrate or sugar that is synthesized is glucose; this is in many cases immediately converted into the osmotically less effective polysaccharide, starch. Because the empirical formula for glucose was shown to be CH_2O , it was designated as a carbohydrate, which literally means hydrated carbon. Therefore, other naturally occurring substances that, before or after hydrolysis, exhibited similar chemical and physical properties were called carbohydrates from the French, "hydrate de carbone."

As a result of a vast amount of research in the field of carbohydrates, it can be concluded that they can be defined as polyhydroxy aldehydes or ketones or condensation products thereof. It is to be implied that such a definition does not hold to the empirical formula $\text{C}_n\text{H}_{2n}\text{O}_n$. This is due to the fact that in some rare and important desoxy sugars, such as 2-desoxyribose, digitoxose, cymarose, rhamnose, etc., that have been found in nature this relationship of C, H and O does not exist.

Carbohydrates furnish a source of energy for both plants and animals. In the form of cellulose, together with lignin they function as the supporting tissues of plants. Their degradation products, by enzymatic means, are

used in the synthesis of fats, proteins and many other naturally occurring products. Sugars, modified or in combination, give rise to or are present in such important naturally occurring substances as vitamin C, riboflavin, co-enzymes I and II, yeast and muscle nucleic acids, a corticometric principle, glycosides, saponins, etc.

Carbohydrates may be classified according to the number of sugar residues* present in the molecule. These divisions in turn may be further subdivided into the number of carbon atoms in each residue, and whether they contain a potential aldehyde or ketone group. Thus, for example, the following classification is possible:

Monosaccharides or Monoses.

TRIOSES ($\text{C}_3\text{H}_6\text{O}_3$). For example, the aldotriose *d*-glyceric aldehyde or glycero-*s*, which occurs as an intermediate in muscle glycolysis and yeast fermentation of glucose, and the ketotriose dihydroxyacetone, which occurs as an intermediate in muscle glycolysis and yeast fermentation of glucose.

TETROSES ($\text{C}_4\text{H}_8\text{O}_4$). For example, the aldotetroses *d*- and *l*-erythrose that have been prepared synthetically and the aldoketoses *d*-erythrulose that has been prepared synthetically.

* The smallest units or molecules into which the carbohydrate can be resolved by acid hydrolytic methods.

PENTOSES ($C_5H_{10}O_5$).

Aldopentoses. *l*-Arabinose occurs naturally in arabans, gums, hemicelluloses, etc. *d*-Xylose occurs in wood gum, mucilages, hemicelluloses, xylans, etc. *d*-Ribose is found in the yeast nucleic acid of animals.

HEXOSES ($C_6H_{12}O_6$).

Aldohexoses. *d*-Glucose, the most abundant sugar of the monosaccharides, occurs chiefly in starch, cellulose, glycogen, sucrose and lactose. *d*-Galactose occurs in galactans, gums, mucilages, hemicelluloses and lactose. *d*-Mannose can be prepared from the reserve polysaccharide found in date seeds and vegetable ivory. It is also found in cherry gum and in several other polysaccharides.

Ketohexoses. *d*-Fructose can be prepared from the polysaccharide inulin found in dahlias and artichokes. It is also found in sucrose. *l*-Sorbitol is found as a fermentation product of the sugar alcohol sorbitol.

Oligosaccharides.

DISACCHARIDES.

Reducing Disaccharides. Maltose (4-*d*-glucopyranosyl- α -*d*-glucopyranoside) is an end-product resulting from the action of diastase upon starch. Cellobiose (4-*d*-glucopyranosyl- β -*d*-glucopyranoside) is one of the hydrolytic products of cellulose. Gentio-biose (6-*d*-glucopyranosyl- β -*d*-glucopyranoside) has been prepared by the hydrolysis of the glycoside amygdalin. Melibiose (6-*d*-glucopyranosyl- α -*d*-glucopyranoside) is obtained upon partial hydrolysis of the trisaccharide raffinose. Lactose (4-*d*-glucopyranosyl- β -*d*-galactopyranoside) is found in milk.

Nonreducing Disaccharides. Sucrose (1- α -*d*-glucopyranosyl- β -*d*-fructofuranoside) is obtained on a commercial scale from sugar cane and sugar beets. It occurs very abundantly in nature.

TRISACCHARIDES.

Nonreducing. Raffinose, which yields galactose, glucose and fructose upon hydrolysis, is found in such plants as cotton, barley, lotus and eucalyptus. Melecitose, upon hydrolysis, yields two molecules of glucose and one of fructose. It is found in Persian manna,

Larix europaea and the manna from *Pseudatsuga Douglasii*. Gentianose, as the name implies, has been found in the roots of *Gentiana lutea*. Upon hydrolysis, it yields two molecules of glucose and one of fructose.

TETRASACCHARIDES.

Nonreducing. Stachyose yields two molecules of galactose and one molecule each of glucose and fructose upon hydrolysis. It is found in *Stachys tuberifera* and in several leguminous seeds.

Polysaccharides or Non Sugars.

PENTOSANS [$(C_5H_8O_4)_n$]. Arabans that yield only arabinose upon hydrolysis are rare. On the other hand, certain gums, such as cherry gum and gum arabic, yield chiefly arabinose upon hydrolysis. Xylans that yield chiefly xylose upon hydrolysis have been obtained from esparto cellulose, deciduous trees and straw.

HEXOSANS [$(C_6H_{10}O_5)_n$]. The glucosans starch, cellulose and glycogen are outstanding examples of a hexosan that is composed of glucose units. The fructosan inulin is found as a reserve carbohydrate in many composites. It can be prepared from the roots of the dahlia and the artichoke and it yields fructose upon hydrolysis. Mannans that yield mannose upon hydrolysis are found in vegetable ivory, date seeds and fenugreek seeds. Galactans are rare.

MIXED POLYSACCHARIDES.

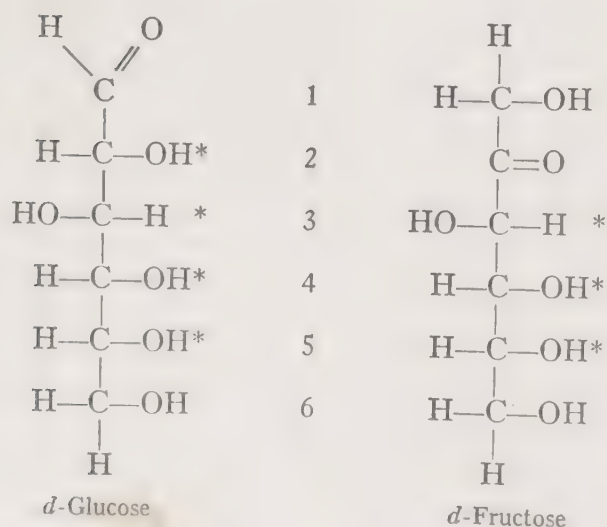
Hemicelluloses, a not too satisfactory term, is used to designate the members of a group of high molecular weight carbohydrates that occur as constant companions of cellulose but differ from it by being considerably more soluble and more easily broken down. This group includes those cell wall polysaccharides that can be extracted by either cold or hot alkali and hydrolyzed to the sugars or uronic acids. They are composed of short chain hexosans and pentosans. Upon hydrolysis, hemicelluloses yield glucose, galactose, mannose, xylose, arabinose, rhamnose and the uronic acids, especially glucuronic and galacturonic. Hemicelluloses are found in almost all plants. They are most

abundant in young tissues, succulents, non-woody plant parts and some seeds.

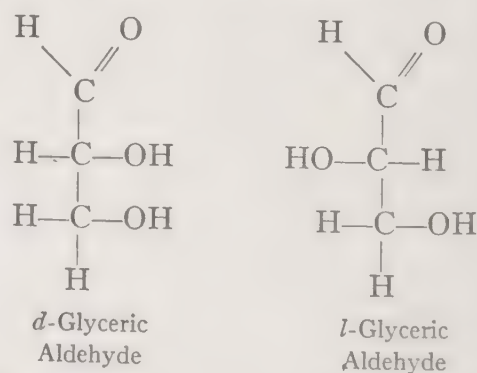
Gums and mucilages are very closely related to the hemicelluloses both in composition and function. They are perhaps more soluble in water than the hemicelluloses, although some of them merely swell up but do not dissolve. Upon hydrolysis, they yield galactose, arabinose, xylose and glucuronic and galacturonic acids.

Pectins, upon hydrolysis, yield chiefly galacturonic acid. They are found as an integral part of the cell framework and structural parts of green plant tissues, such as green leaves, stems and more particularly the fleshy fruits and roots. They are found chiefly in the middle lamella; however, in plants of a succulent nature, they may also diffuse into the cell proper.

Through the brilliant researches of Emil Fischer, the spatial configurations of the alcohol groups in glucose and a number of other simple sugars were elucidated. The carbon atoms in the simple aldoses are designated by arabic numerals, the carbon atom of the aldehyde group having been assigned position 1. In the case of the ketoses, the carbonyl group which is one carbon removed from the end of the chain is given position 2. For example, writing the structural formulae for glucose and fructose in the form of a straight chain, they can be numbered as follows:

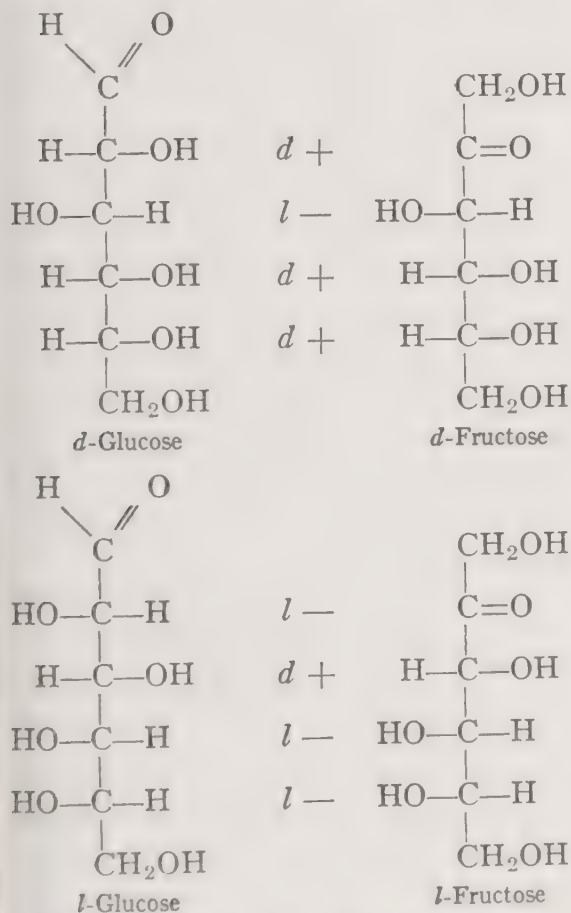


The formula for *d*-glucose shows that carbon atoms 2, 3, 4 and 5 are asymmetric and, therefore, the number of isomers of glucose would be 2^4 or 16. In the case of the ketohexoses, such as fructose carbon atoms 3, 4 and 5 are asymmetric and therefore the number of isomers would be 2^3 or 8. Of the sixteen possible isomers of glucose, eight have mirror images and, being identical in physical and chemical properties except for their effect upon polarized light, are enantiomorphous. Therefore, eight of the isomers would be the *d*-form and eight of them the *l*-form. The designations *d*- and *l*- in the sugar series were unfortunately introduced by Fischer, not to denote the sign of rotation of polarized light but were arbitrarily chosen for the two possible enantiomorphs of glucose. Therefore, other sugars that were structurally related to *d*- or *l*-glucose, in so far as the asymmetry of their carbon atoms were concerned, were likewise called *d*- or *l*-sugars, irrespective of their sign of rotation. Thus, *d*-fructose is levorotatory. A convenient method for assigning sugars into their *d*- and *l*-forms has been suggested by Wohl and Freudenberg. Although the absolute configurations of *d*- and *l*-glyceric aldehyde are not known, their projection formulae can be illustrated as follows:



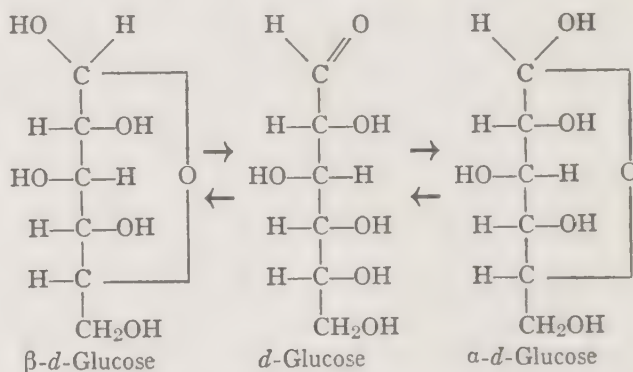
These compounds are the simplest aldose sugars that contain an asymmetric carbon atom. The one in which the asymmetric hydroxyl group is to the right is called *d*-glyceric aldehyde, and its mirror image, or where this hydroxyl group is to the left, is called *l*-glyceric aldehyde. Following this type of nomenclature, the *d*-forms of all

the sugars must have the hydroxyl group to the right on the carbon atom adjacent to the terminal primary alcohol group or the asymmetric carbon atom farthest removed from the carbonyl group. The rest of the molecule must be arranged according to its actual configuration. The converse is true of the *l*-series. All hydroxyls when assigned to the right are called "*d*" hydroxyls and the configurations of the *carbon atoms* containing such hydroxyls are called "*d*." Also, when the hydroxyls are to the left, the "*l*" terminology is employed. For example, writing the structural formulae for *d*-glucose, *d*-fructose, *l*-glucose and *l*-fructose in the form of a straight chain, these positions can be indicated by the letters *d* and *l* or + and —.



Although the usual type of an optically active compound exhibits a fixed degree of specific rotation, such is not the case with *d*-glucose and a number of other sugars. *d*-Glucose, crystallized under certain conditions, when dissolved in water, gave an initial rotation that slowly changed until

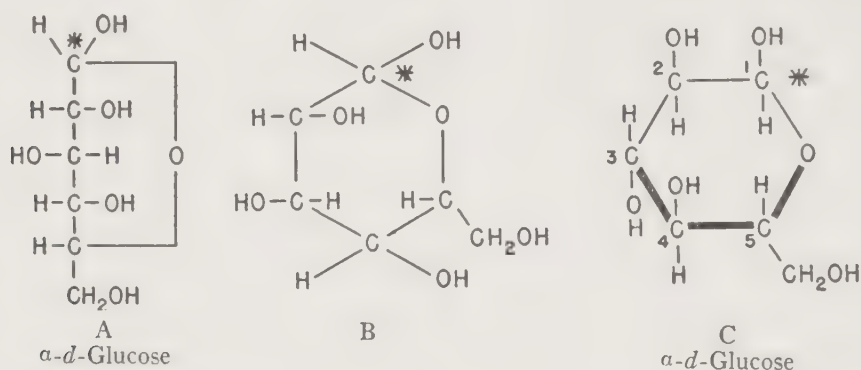
an equilibrium of +52.7 was obtained. The initial rotation may be +19.7 or +113.4, depending upon the method whereby the crystalline glucose is obtained. This phenomenon is called mutarotation and is shown by all the simple sugars and oligosaccharides that have a potential carbonyl group that is not in a glycoside linkage. Therefore, glucose and other simple sugars and some oligosaccharides can exist in two forms. These forms involve an asymmetric center because of their effect on polarized light. This new asymmetric center can only be generated by a hemiacetal formation from the carbonyl group and one of the hydroxyl groups in the remainder of the molecule. In the case of *d*-glucose this can be expressed as follows:



This six-membered ring structure in the sugar series is called the pyranose, amylenoxide or the δ -oxide form. Hudson suggested that the form of *d*-glucose which has the strongest dextrorotatory power be designated as α -*d*-glucose and the other β -*d*-glucose. In the *l*-series the same suggestion was made, thus α -*l*-glucose is the most optically active form. Under certain conditions, some simple sugars have a five-membered oxide ring structure. Some oligosaccharides, polysaccharides, coenzymes, etc., have the five-membered oxide ring structure. This form is called furanose, butylene oxide or the γ -oxide form. The ring structure is the normal form in which sugars exist; however, it is in equilibrium with very small amounts of the free carbonyl form. This equilibrium can shift to completion when sugars are subjected to reactions involving the free carbonyl group. When a sugar crystallizes from solution, it

separates almost entirely in that form which is least soluble under the conditions, the solution equilibrium then shifting to produce more of this isomer. In many cases, the preparation of a sugar in its crystalline α - and β -forms becomes a difficult matter because it is necessary to find conditions under which each form will crystallize. The form in which a sugar exists also influences its degree of sweetness (see lactose).

The cyclic structures of the simple sugars can be better visualized from the following formulae, now described as lactal rings.



The reducing group of glucose is represented by the position marked with an asterisk, and those addenda which are coplanar are shown by the thickened lines. By comparing formula B with formula A it will be seen that the hydroxyl groups and the hydrogen atoms attached to the central chain correspond in each formula may be read off directly from A to B in the same order. In the formulae B and C, the hydroxyls at C₁ and C₂ are in the same plane, the hydroxyl at C₃ and the hydrogen at C₄ are in the same plane, the hydrogens at C₄ and C₅ are in the same plane and the hydroxyl at C₄ and the oxygen bridge are in the same plane. The primary alcohol group can be visualized as a side chain such as is present in benzyl alcohol. For example, its oxidation to a carboxyl group in plants and animals gives rise to the naturally occurring and important uronic acids.

The chemical properties of the carbohydrates are a function of the primary alcohol group when it exists per se, the uncombined

secondary alcohol groups, the alcohol group generated by ring formation and the carbonyl group existing in aqueous solution in equilibrium with the ring structure.

The alcohol groups can be esterified with organic acids such as acetic, propionic, butyric, etc. and with the inorganic acids nitric, phosphoric and sulfuric. They can be condensed with acetone, acetaldehyde, benzaldehyde, etc., to produce the isopropylidene (acetone), ethylidene and benzylidene derivatives. They can be converted to the

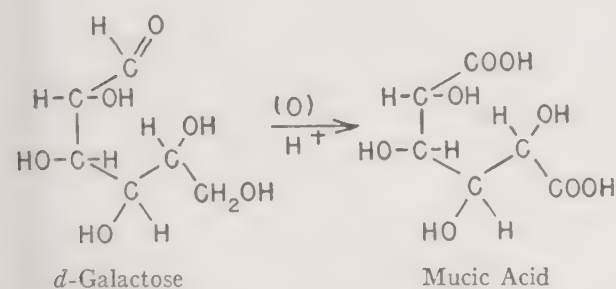
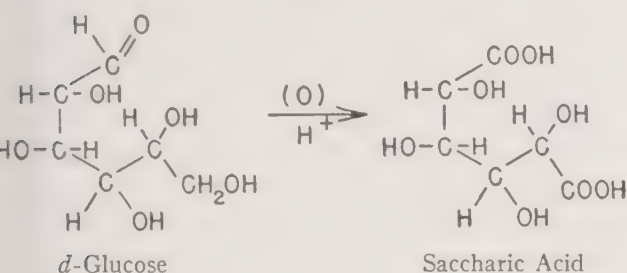
methyl and ethyl ethers.

Under the proper conditions, the terminal alcohol group can be oxidized to a carboxyl group to give the uronic acids. The alcohol group generated by the ring structure can be etherified selectively to give the glycosides (see Chapter 24).

The carbonyl group can be reduced catalytically or with sodium amalgam to give one sugar alcohol in the case of the aldoses and a mixture of two sugar alcohols in the case of the ketoses.

The monosaccharides are reasonably stable under acid conditions, but the oligosaccharides are hydrolyzed to monosaccharides. Sugars are unstable under alkaline conditions and undergo extensive changes in structure. The monosaccharides and the reducing oligosaccharides can be carefully oxidized by chemical methods and by fermentation methods to give the corresponding "onic acids." Thus, glucose is converted to gluconic acid on a commercial scale (see

calcium gluconate). More vigorous oxidation under acid conditions converts monosaccharides and the residues of the oligosaccharides into dicarboxylic acids. In the case of glucose and galactose, they are converted to saccharic and mucic acids, respectively. Mucic acid is so insoluble it can be collected and weighed for the quantitative determination of galactose in the presence of other sugars.

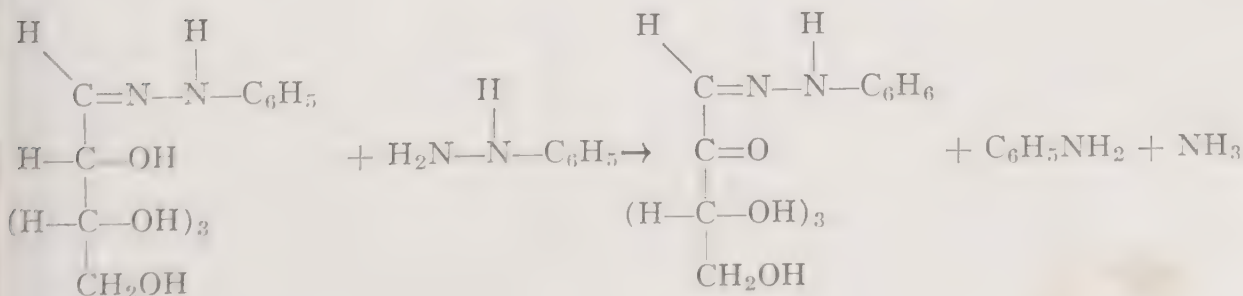
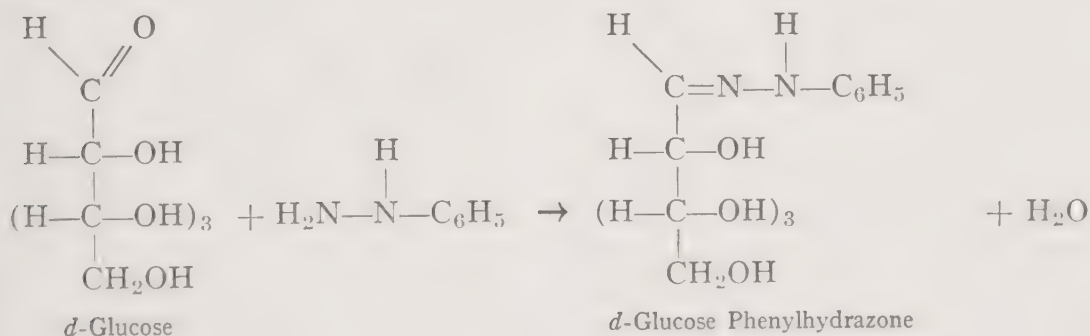


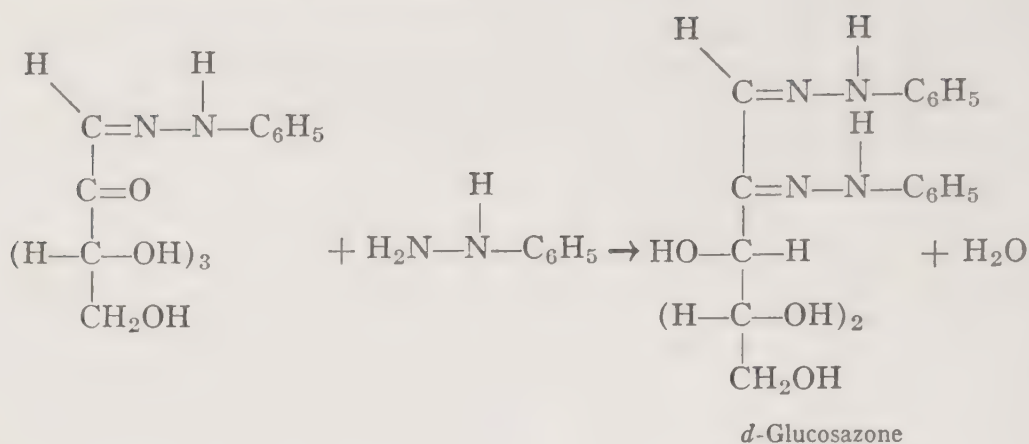
The readiness with which simple sugars are oxidized, particularly under alkaline conditions, is the basis of some qualitative and quantitative procedures. Under alkaline conditions they will reduce cupric salts to cuprous compounds, (Fehling's, Benedict's, Barfoed and Haine's solutions), ammoniacal silver nitrate (Tollen's reagent), picric to picramic acid and 3,5-dinitrosalicylic acid to 3-nitro-5-amino-salicylic acid.

Sugars are readily caramelized when heated, and fructose, the most sensitive sugar in this respect, will caramelize above 70° C.

Dehydrating agents, such as 12 per cent hydrochloric acid, will convert the pentoses quantitatively to furfural, which is of great commercial significance. The aldohexoses yield some hydroxy methyl furfural, and fructose yields levulinic acid, which is now produced on a commercial scale.

The monosaccharides and the reducing oligosaccharides yield oximes, hydrozones and osazones. The osazones, which are yellow, crystalline compounds, are readily prepared and furnish an excellent derivative of sugars which are otherwise difficult to characterize when these sugars are present in mixtures of other substances.



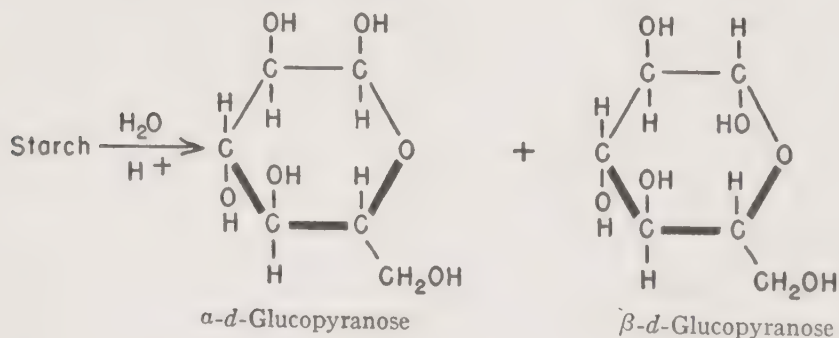


Glucose, fructose and mannose give the same osazone; therefore, the configurations about carbon atoms 3, 4 and 5 in these compounds must be the same.

Dextrose (*d*-Glucose) U.S.P. (Grape sugar, Glucose). "Dextrose is a sugar usually obtained by the hydrolysis of starch." It can be either α -*d*-glucopyranose or β -*d*-glucopyranose or a mixture of the two. A large amount of the dextrose of commerce, whether crystalline or syrupy, is usually obtained by the acid hydrolysis of corn starch, although other starches can be used.

Aqueous solutions of glucose can be sterilized in an autoclave.

Glucose can be used as a ready source of energy in various forms of starvation. It is the sugar found in the blood of animals and in the reserve polysaccharide glycogen which is present in the liver and muscle. It can be used in solution intravenously to supply fluid and to sustain the blood volume temporarily. It has been used in the management of the shock which may follow the administration of insulin used in the treatment of



Although some free glucose occurs in plants and animals, most of it occurs in starches, cellulose, glycogen and sucrose. It also is found in other polysaccharides, oligosaccharides and glycosides.

"Dextrose occurs as colorless crystals or as a white, crystalline or granular powder. It is odorless, and has a sweet taste. One Gm. of Dextrose dissolves in about 1 cc. of water and in about 60 cc. of alcohol. It is more soluble in boiling water and in boiling alcohol."

schizophrenia. This, because a "hypoglycemia" results from the use of insulin in this type of therapy, and it can be brought to normal by the use of dextrose intravenously. When dextrose is used intravenously, its solutions (5 to 50 per cent) usually are made with physiologic salt solution or Ringer's solution. The dextrose used for intravenous injection must conform to the U.S.P. requirements for Dextrose.

OFFICIAL OCCURRENCE

U.S.P.

Dextrose & Sodium Chloride Injection

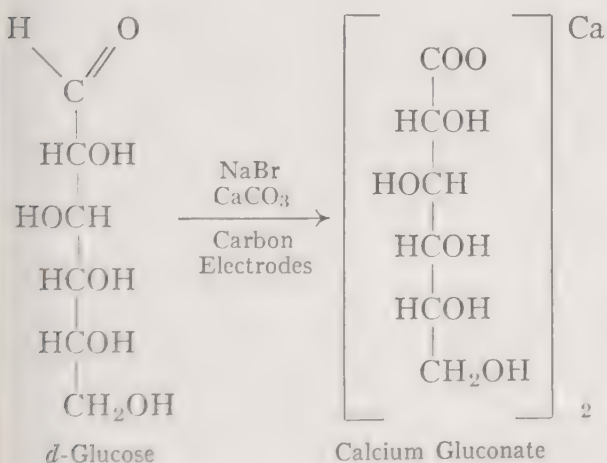
Dextrose Injection

"Liquid Glucose (Glucose), U.S.P. is a product obtained by the incomplete hydrolysis of starch." It consists chiefly of dextrose (*d*-glucose, $C_6H_{12}O_6$), with dextrans, maltose and water. This glucose usually is prepared by the partial acid hydrolysis of corn starch and, hence, the common name corn syrup and other trade names refer to a product similar to Liquid Glucose. The official product contains not more than 21 per cent of water.

"Liquid Glucose is a colorless or yellowish, thick, syrupy liquid. It is odorless, or nearly so, and has a sweet taste. Liquid glucose is very soluble in water, but is sparingly soluble in alcohol."

Liquid Glucose is used extensively as a food (sweetening agent) for both infants and adults. It is used in the massing of pills, in the preparation of pilular extracts, etc. It is not to be used intravenously.

Calcium Gluconate U.S.P. "contains not less than 8.8 per cent of calcium, corresponding to not less than 99 per cent of $Ca(C_6H_{11}O_7)_2 \cdot H_2O$." The gluconic acid used in the preparation of calcium gluconate can be prepared by the electrolytic oxidation of glucose as follows:



Gluconic acid is produced on a commercial scale by the action of a number of fungi, bacteria and molds upon 25 to 40 per cent solutions of glucose. The fermentation is

best carried out in the presence of calcium carbonate and oxygen to give almost quantitative yields of gluconic acid. A number of organisms can be used, for example, *Bacillus oxydans*, *B. aceti*, *B. acetosum*, *B. industrium*, *B. gluconicum*, *B. xylinum*, *Hoshigaki* var. *rosea* or *industrium* var. *Hoshigaki* and *Penicillium chrysogenum*. The fermentation is complete in 8 to 18 days.

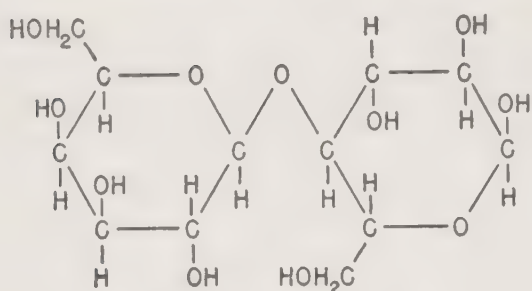
"Calcium gluconate occurs as a white, crystalline or granular powder without odor or taste. It is stable in air. Its solutions are neutral to litmus paper. One Gm. of Calcium Gluconate dissolves slowly in about 30 cc. of water, and in 5 cc. of boiling water. It is insoluble in alcohol and in many other organic solvents."

Calcium gluconate will be decomposed by the mineral acids and other acids that are stronger than gluconic acid. It is incompatible with soluble sulfates, carbonates, bicarbonates, citrates, tartrates, salicylates and benzoates.

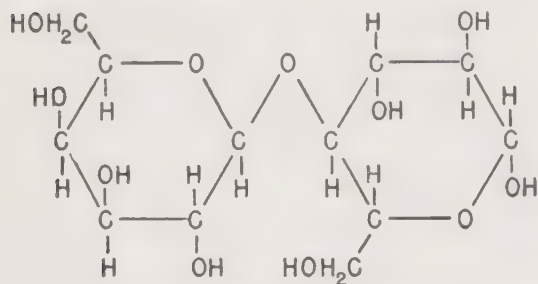
Calcium gluconate supplies the need for a soluble, nontoxic well-tolerated form of calcium therapy that can be employed orally, intramuscularly or intravenously. Calcium therapy is indicated in such conditions as parathyroid deficiency (tetany), when calcium is the limiting factor in decreased clotting time of the blood and general calcium deficiency.

"Lactose (Saccharum Lactis, Milk Sugar), U.S.P. is a sugar obtained from milk." Lactose is a by-product of whey, which is the portion of milk that is left after the fat and casein have been removed for the production of butter and cheese. Cows' milk contains 2.5 to 3 per cent lactose, whereas, in other mammals, it is present in 3 to 5 per cent concentrations. Although common lactose is a mixture of the alpha and beta forms, the pure beta form is sweeter than the slightly sweet-tasting mixture.

"Lactose occurs as white, hard, crystalline masses or as a white powder. It is odorless, and has a faintly sweet taste. It is stable in air, but readily absorbs odors. Its solutions are neutral to litmus paper. One



Galactose Glucose
 α -Lactose
 α -4-*D*-Glucopyranosyl- β -*D*-galactopyranoside



Galactose Glucose
 β -Lactose
 β -4-*D*-Glucopyranosyl- β -*D*-galactopyranoside

Gm. of Lactose dissolves in 5 cc. of water, and in 2.6 cc. of boiling water. Lactose is very slightly soluble in alcohol and is insoluble in chloroform and in ether."

Lactose is readily hydrolyzed in acid solutions to yield one molecule each of *D*-glucose and *D*-galactose. It reduces Fehling's solution.

Lactose is used as a diluent in tablets and powders and as a nutrient for infants.

β -Lactose when applied locally to the vagina brings about a desirable lower pH. The lactose probably is fermented, with the production of lactic acid.

Maltose or malt sugar, 4-*D*-glucopyranosyl- α -*D*-glucopyranoside, is an end-product of the enzymatic hydrolysis of starch by the enzyme diastase. It is a reducing disaccharide that is fermentable and is hydrolyzed by acids or the enzyme maltase to yield two molecules of glucose.

Maltose is a constituent of Malt Extract N.F. and is used for its nutritional value for infants and adult invalids.

"Malt Extract N.F. is a product obtained by extracting malt, the partially and arti-

ficially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam. *Gramineae*). Malt extract contains maltose, dextrins, a small amount of glucose and amylolytic enzymes.

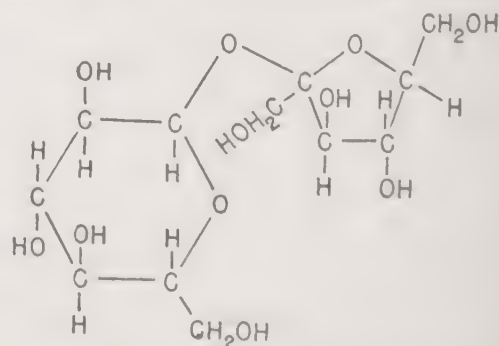
Malt extract is used in the brewing industry because of its enzyme content which converts starches to fermentable sugars. It is also used in infant feeding for its nutritive value and laxative effect.

Dextrins are obtained by the enzymatic (diastase) degradation of starch. These degradation products vary in molecular weight in the following decreasing order: amylo-dextrin, erythodextrin and achroodextrin. Lack of homogeneity precludes the assignment of definite molecular weights. With the decrease in molecular weight, the color produced with iodine changes from blue to red to colorless.

Dextrin occurs as a white, amorphous powder that is incompletely soluble in cold water but freely soluble in hot water.

Dextrins are used extensively as a source of readily digestible carbohydrate for infants and adult invalids. They often are combined with maltose or other sugars.

Sucrose (*Saccharum*, Sugar) U.S.P. (Cane Sugar, Beet Sugar). "Sucrose is a sugar obtained from *Saccharum officinarum* Linné (Fam. *Gramineae*), *Beta vulgaris* Linné (Fam. *Chenopodiaceae*), and other sources." Sugar cane (15 to 20 per cent sucrose) is expressed, and the juice is treated with lime to neutralize the plant acids. The water-soluble proteins are coagulated by heat and are removed by skimming. The resultant liquid is decolorized by means of



Sucrose
 α -4-*D*-Glucopyranosyl- β -*D*-fructofuranoside

charcoal and concentrated. Upon cooling, the sucrose crystallizes out. The mother liquor, upon concentration, yields more sucrose and brown sugar and molasses.

"Sucrose occurs as colorless or white crystals, crystalline powder. It is odorless, has a sweet taste, and is stable in air. Its solutions are neutral to litmus. One Gm. of Sucrose dissolves in 0.5 cc. of water and in 170 cc. of alcohol."

Sucrose does not respond to the tests for reducing sugars, i.e., reduction of Fehling's solution, etc. It readily is hydrolyzed, even in the cold, by acid solutions to give one molecule each of *d*-glucose and *d*-fructose. This hydrolysis also can be effected by the enzyme invertase. Sucrose carmelizes at about 210° C.

Sucrose is used in the preparation of syrups and as a diluent and sweetening agent in a number of pharmaceutical preparations, e.g., troches, lozenges, powdered extracts and Lunosol, a colloidal silver preparation. In a concentration of 0.8 Gm. per cc., sucrose is used as a sclerosing agent.

Starch (Corn Starch) U.S.P. "consists of the granules separated from the grain of *Zea mays* Linné (Fam. *Gramineae*)."
Corn, which contains about 75 per cent dry weight of starch, is first steeped with sulfurous acid and then milled to remove the germ and seed coats. It is then milled with cold water, and the starch is collected and washed by screens and flotation. Starch is a high-molecular-weight carbohydrate composed of 10 to 20 per cent of a hot-water-soluble "amylose" and 80 to 90 per cent of a hot-water-insoluble "amylopectin." Amylose is completely hydrolyzed to maltose by the enzyme β -amylase, whereas amylopectin is only incompletely (60 per cent) hydrolyzed to maltose. The glucose residues are in the form of branched chains in the amylopectin molecule. The chief linkages of the glucose units in starch are α -1, 4. This, because β -amylase hydrolyzes only alpha linkages and maltose is 4-*d*-glucopyranosyl- α -*d*-glucopyranoside.

"Starch occurs as irregular, angular, white

masses or as a fine powder, and consists chiefly of polygonal, rounded, or spheroidal grains from 3 to 35 microns in diameter and usually with a circular or several-rayed central cleft." It is odorless and has a slight, characteristic taste. Starch is insoluble in cold water and in alcohol.

Amylose gives a blue color on treatment with iodine, and amylopectin gives a violet to red-violet color.

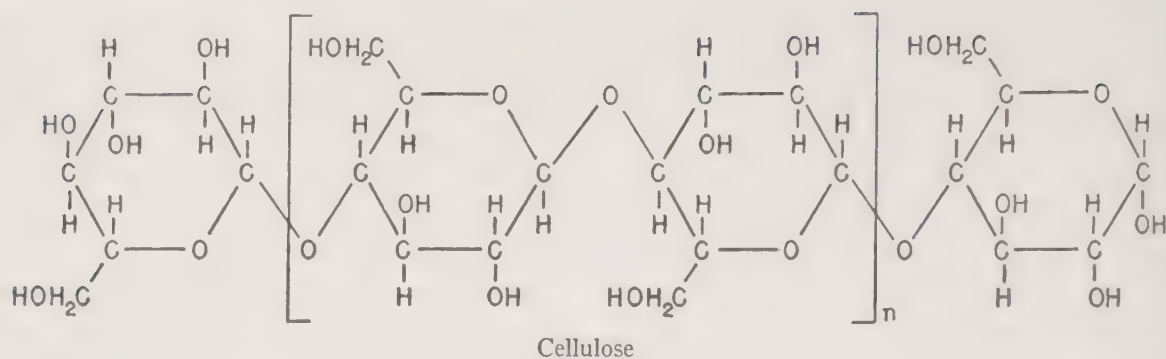
Starch is used as an absorbent in starch pastes, as an emollient in the form of a glycerite and as a diluent in pills, solid extracts, tablets and powders.

OFFICIAL OCCURRENCE U.S.P.	PER CENT STARCH GLYCERITE
	GLYCERITE
Starch Glycerite	10.0

Cellulose is the name generally given to a group of very closely allied substances rather than to a single entity. The celluloses are anhydrides of β -glucose, possibly existing as long chains that are not branched, consisting of 100 to 200 β -glucose residues. These chains may be cross linked by residual valences (hydrogen bonds) to produce the supporting structures of the cell walls of plants. The cell walls found in cotton, pappi on certain fruits, etc., are the purest forms of cellulose; however, because they are cell walls, they enclose varying amounts of substances that are proteinaceous, waxy, fatty, etc. These, of course, must be removed by proper treatment in order to obtain pure cellulose. Cellulose from almost all other sources is combined by ester linkages, glycoside linkages, etc., with encrusting substances such as lignin, hemicelluloses, pectins, etc. These can be removed by steam under pressure, weak acid or alkali solutions, and sodium bisulfite and sulfurous acid. Plant celluloses, especially those found in wood, can be resolved into β -cellulose, which is soluble in 17.5 per cent sodium hydroxide, and alkali-insoluble α -cellulose. The cellulose molecule can be depicted in part as shown on the next page.

Methyl and ethyl cellulose ethers* can be

* Examples of these are the commercial products Methocel and Ethocel.



prepared by the action of methyl and ethyl chlorides or methyl and ethyl sulfates, respectively, upon cellulose that has been previously treated with alkali. Purification is accomplished by washing the reaction product with hot water. The degree of methylation or ethylation can be controlled to yield products that vary in their viscosities when they are in solution. Six viscosity types are produced commercially.

Methylated celluloses of a lower methoxy content are soluble in cold water, but in contrast to the naturally occurring gums, they are insoluble in hot water and are precipitated out of solution at or near the boiling point. With the increase in methoxy content, the solubility in water decreases until complete water insolubility is reached.

Methyl cellulose resembles cotton in appearance and is neutral, odorless, tasteless and inert. It is soluble in water to give clear, colorless solutions. Methyl cellulose is insoluble in most of the common organic solvents.

Methyl cellulose solutions are stable over a wide range of pH (2 to 12) with no apparent change in viscosity. The solutions do not ferment and will carry large quantities of univalent ions such as iodides, bromides, chlorides and thiocyanates. However, smaller amounts of polyvalent ions such as sulfates, phosphate, carbonate, and tannic acid or sodium formaldehyde sulfoxylate will cause precipitation or coagulation.

The methyl celluloses are used as substitutes for the natural gums and mucilages such as gum tragacanth, gum karaya, chondrus or quince seed mucilage. In general,

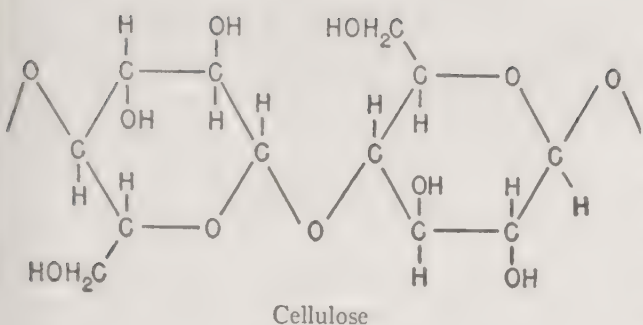
methyl cellulose of the 1,500 or 4,000 cps. viscosity type is the most useful as a thickening agent when used in 2 to 4 per cent concentrations. For example, a 2.5 per cent concentration of a 4,000 cps. type methyl cellulose will produce a solution with a viscosity obtained by 1.25 to 1.75 per cent tragacanth.

The ethyl celluloses resemble the methyl celluloses in their properties.

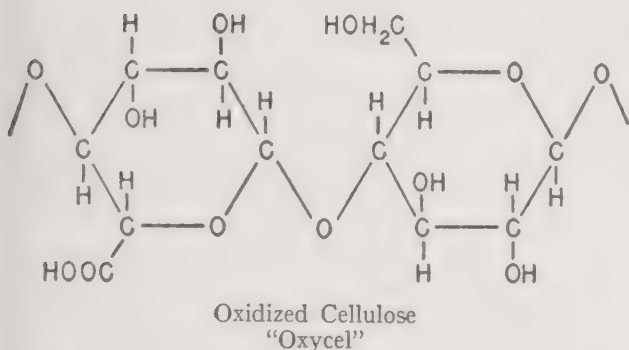
Purified Cotton (Absorbent Cotton) U.S.P. "is the hair of the seed of cultivated varieties of *Gossypium hirsutum* Linné, or of other species of *Gossypium* (Fam. *Malvaceae*), freed from adhering impurities, deprived of fatty matter, bleached and sterilized."

Oxycel is cellulose in which about half of the terminal primary alcohol groups of the glucose residues have been converted into carboxyl groups.* The product is, therefore, possibly a synthetic polyanhydrocellobiuronide. It is prepared by the action of nitrogen dioxide, or a mixture of nitrogen dioxide and nitrogen tetroxide, upon cellulose fabrics at ordinary temperatures.¹ Because cellulose is a high molecular weight carbohydrate composed of glucose residues joined 1,4- to each other in their beta forms, this reaction can only be depicted as follows upon the cellulose molecule in part.

* If all the terminal primary alcohol groups are converted to carboxyl groups (25 per cent CO_2), the product is too brittle (friable) and too readily soluble to be of use. A product that analyzes for about 14 per cent CO_2 is the most desirable.



↓ Nitrogen Dioxide
Nitrogen Tetraoxide
21° C.



The oxidized cellulose fabric, such as gauze or cotton resembles the parent substance. It is soluble in 2 per cent sodium hydroxide and in other basic substances. In weakly alkaline solutions, it swells and becomes translucent and gelatinous. When wet with blood, it becomes slightly sticky and swells, forming a dark brown, gelatinous mass. Oxycel cannot be sterilized by autoclaving. Special methods are needed to render it sterile.

Oxycel has noteworthy hemostatic properties. However, when it is used in conjunction with thrombin, it should be neutralized previously with a solution of sodium bicarbonate. Oxycel is used in various surgical procedures in much the same way as gauze or cotton by direct application to the oozing surface. Except when used for hemostasis, Oxycel is not recommended as a surface dressing for open wounds. Oxycel implants in connective tissue, muscle, bone, serous and synovial cavities, brain, thyroid, liver, kidney and spleen were completely absorbed in varying lengths of time, depending on the amount of material introduced, the extent of

operative trauma and the amount of blood present.²

Proxylin (Soluble Guncotton), U.S.P. "is a product obtained by the action of nitric and sulfuric acids on cotton, and consists chiefly of cellulose tetranitrate [$C_{12}H_{16}O_6(NO_3)_4$]." The glucose residues in the cellulose molecule contain three free hydroxyl groups which can be esterified. Two of these three hydroxyl groups are esterified to give the official pyroxylin, and, therefore, it is really a dinitrocellulose or cellulose dinitrate which conforms to the official nitrate content.

"Pyroxylin occurs as a yellowish white, matted mass of filaments, resembling raw cotton in appearance, but harsh to the touch." It is exceedingly inflammable and decomposes when exposed to light, with the evolution of nitrous vapors and leaving a carbonaceous residue. "Pyroxylin dissolves slowly but completely in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol."

In the form of collodion and flexible collodion it is used for coating purposes per se or in conjunction with certain medicinal agents.

OFFICIAL OCCURRENCE	PER CENT PYROXYLIN
U.S.P.	
Collodion	4.0
Flexible Collodion	3.8
N.F.	
Salicyclic Collodion	3.6

Metamucil N.N.R. contains about 50 per cent of a highly purified hemicellulose that is obtained from the outer seed coat of blonde psyllium seed, *Plantago ovata* Forsk. The remaining 50 per cent is anhydrous dextrose together with small amounts of sodium bicarbonate, monobasic potassium phosphate, citric acid and benzyl benzoate.

Mucilose is a highly purified hemicellulose obtained from the outer seed coat of *Plantago loeflingii*.

The mucilages, which are hemicelluloses, are found in the outer seed coats of the various species of *Plantago*, for example, *Plantago ovata*, *P. psyllium*, *P. lanceolata*,

P. loeflingii and *P. arenaria*, have similar compositions and properties. They³ yield *d*-galacturonic acid, *d*-galactose, *l*-arabinose and *d*-xylose upon hydrolysis. Their composition depends upon the way in which they are prepared, if, for example, by water extraction methods or in some cases mechanical methods. The mucilage content may be as high as 20 per cent of the dry weight of the seed.

The mucilages from the *Plantago* species are used to provide a soft, bland bulk, that exerts a gentle, stimulating effect upon the bowel. These mucilages are not digestible and do not interfere with the assimilation of food or vitamins. They are used in spastic constipation, mucous colitis, atonic colitis and ulcerative colitis conditions.

Acacia (Gum Arabic) U.S.P. "is the dried gummy exudation from the stems and branches of *Acacia Senegal* (Linné), Willdenow or of some other African species of *Acacia* (Fam. *Leguminosae*).² Gum arabic is a mixture of the calcium, magnesium and potassium salts of a mixed polysaccharide called arabic acid that has a molecular weight of 1,000 to 1,200. Upon mild acid hydrolysis, (0.01N sulfuric acid) arabic acid yields *l*-arabinose, *l*-rhamnose, and 3-*d*-galactoside-*l*-arabinose plus a branched-chain nucleus that appears to be homogenous and is composed of galactose and glucuronic acid residues in the proportions of three to one.⁴ The carboxyl groups of the glucuronic acid residues are responsible for the acidic properties of gum arabic.

Acacia occurs as spheroidal tears, or as a white to yellowish white powder. It is insoluble in alcohol, but is almost completely soluble in twice its weight of water at room temperature, the resulting solution flowing readily. It is acid to litmus.

Acacia is used as a demulcent and as an emulsifying agent and vehicle in the preparation of emulsions, pills and troches. It can be used to restore the normal colloidal osmotic pressure in the treatment of nephrotic edema, in which case sodium arabinates is administered intravenously as a 6 per cent

solution in physiologic salt solution. It also can be used intravenously in the treatment of posthemorrhagic shock.

OFFICIAL OCCURRENCE	PER CENT ACACIA
U.S.P.	
Acacia Mucilage	35.0
N.F.	
Acacia Syrup	10.0

Tragacanth (Gum Tragacanth) U.S.P. "is the dried gummy exudation from *As-tragalus gummifer* Labillardiere, or other Asiatic species of *Astragalus* (Fam. *Legum-inosae*).² This plant gum is a complex mixture of a polyuronide (tragacanthic acid), a galactoaraban and a glycosidic substance, probably steroidal in nature.⁵ Tragacanthic acid has a branched chain structure similar to that of arabic acid. The repeating residue is galacturonic acid (pyranose and linked C₁ to C₄ as in pectic acid) that is terminated by *d*-xylopyranose and the rare *l*-fucopyranose sugars. The galactoaraban contains arabinose and galactose.

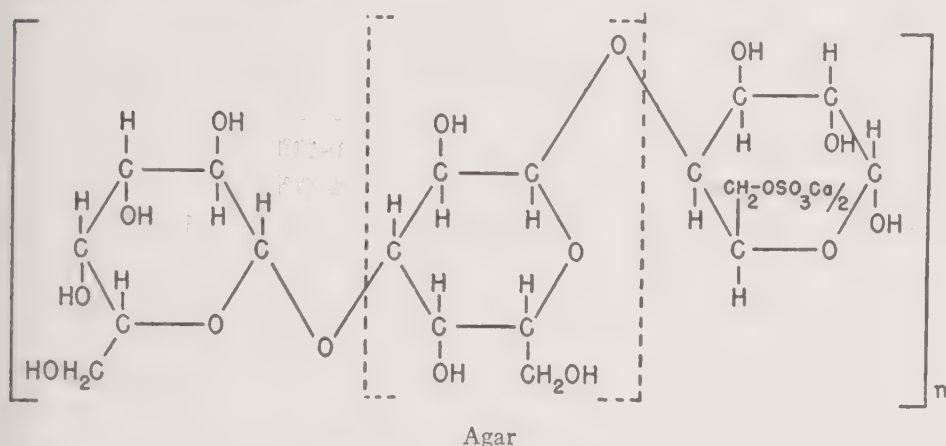
Tragacanth occurs as white or weak yellow, flattened, lamellated, frequently curved fragments or in straight or spirally twisted linear pieces or as a white to yellowish white powder. One gram of tragacanth in 50 cc. of water swells and forms a smooth, nearly uniform, stiff opalescent mucilage free from cellular fragments.

Tragacanth is used in hand lotions, as a demulcent, as an emulsifying agent and as a suspending agent for heavy powders in liquid preparations. It is also used as an adhesive in pills, troches, etc.

OFFICIAL OCCURRENCE	PER CENT TRAGACANTH
U.S.P.	
Tragacanth Mucilage	6.0

Agar (Agar-Agar) U.S.P. "is the dried hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gail-lon (Fam. *Gelidiaceae*) and from related red algae (Class *Rhodophyceae*).² A number of agars, either identical in structure or closely related in structure, can be extracted with hot water from *Gelidium cartilagineum*, *Gelidium latifolium*, *Gelidium crinale* and *Gracilaria confervoides*. Agar⁶ is composed

chiefly of the calcium salt of the sulfuric acid ester of a linear polygalactose, in which the repeating unit is composed of *d*-galactopyranose residues terminated at the reducing end by one residue (molecule) of *l*-galactose. The *d*-galactose residues (molecules) are joined to each other by 1,3-glycosidic linkages, whereas the reducing end member, *l*-galactose, is attached to the chain through position 4. The *l*-galactose is esterified at carbon atom six with sulfuric acid. A tentative formula in part to satisfy the above relationships can be depicted as follows, even though the sulfur content is higher than that found in related agars.



Agar occurs unground in bundles consisting of thin, membranous agglutinated pieces, as cut, flaked or granulated pieces or as a white to yellowish white or pale yellow powder. Agar is soluble in boiling water but insoluble in cold water, in alcohol and in organic solvents.

Agar forms gels with water and can absorb at least 5 times its weight of water. This property of gel formation together with its indigestibility is the basis of the use of agar to furnish bulk in the treatment of chronic constipation. It is also used in conjunction with mineral oil and phenolphthalein. Agar has been used extensively in culture media in bacteriology.

Chondrus (Irish-Moss) N.F. "is the dried bleached plant of *Chondrus crispus* (Linné) Stackhouse, or of *Gigartina mamillata* (Goodenough et Woodward) J. Agardh (Fam. *Gigartinaceae*). These sea algae, like

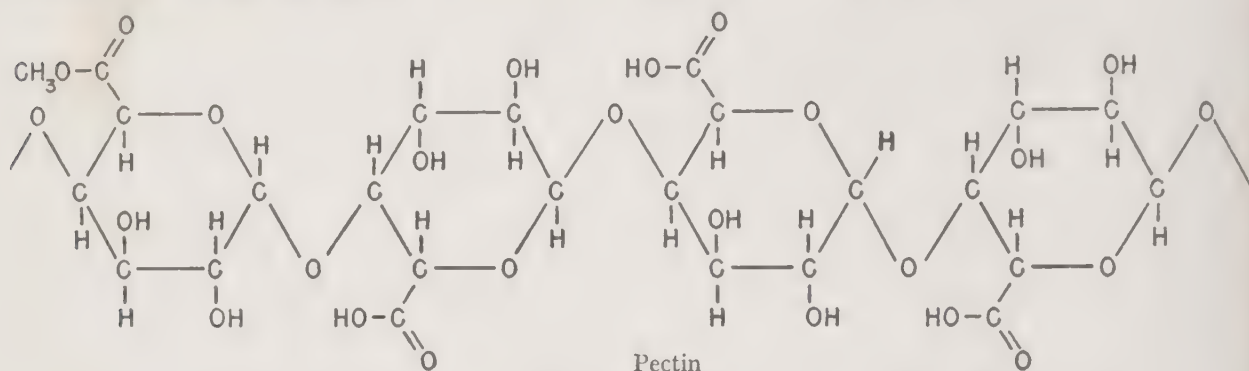
Gigartina stellata, yield a polysaccharide, composed chiefly of galactose residues that are esterified with potassium acid sulfate.⁷ This polysaccharide has mucilagenous properties.

OFFICIAL OCCURRENCE U.S.P.	PER CENT CHONDRUS
Chondrus Mucilage	3.0

Pectin N.F. "is a purified carbohydrate product obtained from the dilute extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic

acids." Pulped apple pomace or cull lemons are first washed and then cooked with a dilute mineral or organic acid, usually in the presence of sulfurous acid. These operations liberate any combined pectin and bring it into solution quite free of soluble sugars. The mixture is filtered, and the filtrate is concentrated to a syrup which may be marketed as such or used in the preparation of a solid product. When lemon albedo extracts are used, the pectin is precipitated with aluminum sulfate and ammonia. The aluminum is removed from the dried precipitate by washing with acidified alcohol. Solid pectin also may be prepared by the addition of alcohol to the syrup described above to effect a precipitation of the pectin or the syrup may be dried as a thin film on a drum. Pectin is composed of galacturonic acid residues with each fourth residue being

esterified with methyl alcohol.*⁸ The pectin molecule has a rodlike structure⁹ and can be depicted in part as follows:



Pectin, when present in plants, usually is combined with calcium and magnesium.

Pectins occur in leaves, stems, roots and fleshy fruits. The pectin content of the fleshy portion of many fruits and green leaves may be as high as 20 or 30 per cent of the total dry weight. Dried sugar-beet pulp and the albedo (white portion) of orange peelings often contain 50 per cent pectins. Lemon peels and apple pulp are also rich in pectin.

Pectin occurs as a coarse or fine powder, yellowish white in color, almost odorless, and with a mucilaginous taste. Pectin is almost completely soluble in twenty parts of water at 25°, forming a viscous, opalescent, colloidal solution which flows readily and is acid to litmus paper. It is insoluble in alcohol or in diluted alcohol, and in other organic solvents. Pectin dissolves in water more readily if first moistened with alcohol, glycerin, or simple syrup, or if first mixed with 3 or more parts of sucrose.

Jellies are made possible by the fact that dilute aqueous solutions of pectin can be induced to set into a clear firm jell in the presence of a medium that contains a high concentration of sugar and a definite, optimal concentration of hydrogen ions. The methyl ester linkages in pectin are readily saponified by means of alkali even at room temperature to yield a gel or semi-gel. Acidification of such saponified pectin gives pectic acid, which separates to form a voluminous, colorless, gelatinous precipitate. Such treatment or conditions destroy the

usefulness of pectin. Heating acidified pectin solutions for prolonged periods of time also produces pectic acid.

Pectin is usually sold according to its "jelly grade," which refers to the number of pounds of sucrose that one pound of pectin can "carry" in a jelly of standard acidity and water content. Therefore, a "100 jelly grade" means that one pound of such a pectin will produce a satisfactory jelly with 100 pounds of sugar, when the finished mixture contains 65 per cent sugar and the proper acidity.† Pure pectins usually have a jelly grade of 180 to 300. The commercial grade of pectin is standardized to a value of not more than 150. This standardization is accomplished by the addition of dextrose or other sugars and some preparations contain sodium citrate or other buffer salts. Such products are not recognized by the N.F.

Pectin is not digested by humans, but passes into the intestinal tract, where it appears to be of value in the treatment of intestinal disorders such as diarrhea and dysentery. Pectin in the form of pastes appears to have bacteriostatic activity and is used in the treatment of indolent ulcers and deep wounds.

OFFICIAL OCCURRENCE	PER CENT PECTIN
N.F.	
Pectin Paste	7.5
Thin Pectin Paste	3.5

Sodium Alginate N.F. "is the purified carbohydrate product extracted from giant brown seaweeds by the use of dilute alkali."

* The N.F. states pectin should contain not less than 7 per cent methoxyl groups.

† One per cent tartaric acid.

The horsetail kelp, *Laminaria digitata*, and the broad-leaf or sugar kelp, *Laminaria saccharina*, are harvested as raw materials from the European and American coasts of the Atlantic ocean. The giant kelp, *Macrocystis pyrifera*, is collected from the Pacific coast of the United States for the production of sodium alginate. The chopped and shredded seaweed is first leached with acid water to remove soluble salts and free the alginic acid from its calcium and magnesium salts. It is then digested with alkali or alkali carbonates to dissolve the alginic acid that is present in the seaweed. The resulting alkaline aqueous solution is bleached or decolorized. Acidulation of this solution yields insoluble alginic acid, which is subjected to further purification by washing with acid water and alcohol. The alginic acid is reconverted into the sodium salt as a final step in its preparation.

Alginic acid is a polymannuronide in which the *d*-mannuronic acid residues have a beta linkage. It, therefore, has a free carboxyl group for each sugar residue.

"Sodium alginate occurs as a nearly odorless and tasteless, coarse or fine powder, yellowish white in color." It is soluble in water to give a viscous, colloidal solution. It is insoluble in the common organic solvents.

Solutions of sodium alginate yield precipitates with polyvalent cations. Acidulation of solutions of sodium alginate yield voluminous gelatinous precipitates.

Sodium alginate is used because of its properties as an emulsifying, suspending, jellying, thickening and body agent. It is used as a stabilizer for ice cream and is used in other food products. It can be used in greaseless lubricating jellies, in hand lotions and in other pharmaceuticals which require thickening agents.

Heparin Sodium N.N.R. The existence of an anticoagulant material in liver was first demonstrated by McLean in 1916 while working in Howell's laboratory at Johns Hopkins. In 1918, Howell and Holt named the substance heparin (Gr., *hepar-*

liver) to indicate its origin and source. Since then it has been shown to be present in practically all types of animal tissue, but predominantly in lung and liver tissue.

Heparin may be prepared commercially from lung and liver employing the procedure of Kuizenga and Spaulding¹⁰ combined with suitable methods for purifying the isolated heparin. The sodium salt is white and is freely soluble in water but poorly soluble in alcohol. It is stable to heat and solutions may be sterilized by autoclaving.

The structure of heparin is not known with certainty. Jorpes, at the Caroline Institute in Stockholm, first proposed it to be a chondroitin polysulfuric acid because it contained 2-amino glucose instead of 2-amino galactose. Hydrolytic experiments have yielded acetic acid, sulfuric acid, 2-aminoglucose and glycuronic acid. These are presumably the four units comprising heparin. The acetic acid occurs in the form of acetylated amino groups, and the sulfuric acid is probably half esterified with primary alcohol groups. The units are thought to be connected in chains similar to those in cellulose.

Heparin occurs as the sodium salt and its potency is expressed in units. It is supplied by the manufacturers in 10 cc. vials each containing 10 mgm. per cc. of the sodium salt in solution. Each mgm. of the dry material is equivalent to at least 100 units in anticoagulant activity. There has been some confusion concerning "units" of heparin because of the fact that as its purity increased, the meaning of a unit also changed. The usual unit is the "Toronto unit," which represents the anticoagulant activity of 0.01 mg. of the pure crystalline barium salt of heparin. According to the N.N.R. (1947), the standard of potency is the Provisional International Standard which is a dried heparin sodium (prepared from the Toronto barium salt) to which has been assigned a potency of 130 units per mgm. The Toronto unit and the international unit are equivalent since 130 mgm.

of the sodium salt is theoretically equivalent to 100 mgm. of the barium salt.

Heparin, as previously indicated, is a blood anticoagulant and has little other biologic action. The exact mechanism whereby it prevents coagulation is not known and has been the object of much pharmacologic investigation. It is not active orally, and is usually administered intravenously because intramuscular or subcutaneous injection might cause bleeding at the site of injection. Recently, however, heparin has been administered subcutaneously in Pitkin's menstruum,¹¹ which to be most effective consists of gelatin (18 per cent), dextrose (8 per cent), glacial acetic acid (0.5 per cent) and water (q.s.). The purpose of this vehicle is to slow down and equalize the release of the heparin into the tissues. Ordinarily, heparin acts quickly following injection, its action being apparent in approximately 10 minutes. Its effect is over in approximately one to two hours, i.e., the blood coagulation time returns to normal (2 to 6 minutes for blood from skin puncture or 4½ minutes for blood withdrawn from a vein). The usual clotting time which it is desirable to attain with heparin is from 15 to 20 minutes. The effect of heparin may be terminated rapidly by infusion of fresh whole blood. The fast onset of action and short duration of action are in contrast to the delayed but longer lasting effect of Dicoumarol (q. v.), a synthetic blood anticoagulant. Note should be made of the fact that digitalis inhibits the action of heparin and should not be administered during heparinization.

The anticoagulant effect, of course, is the basis for its use medicinally. Its greatest use has been in the prevention and arrest of thrombosis. It has been used successfully in mesenteric thrombosis, cavernous sinus thrombosis, thrombosis of the central vein of the retina and routinely as a post-surgical preventative of thrombotic conditions. It does not destroy a thrombus, but it prevents the thrombus from increasing in size and in so doing reduces the pos-

sibility of an embolism. It has been used experimentally with encouraging results in the treatment of frostbite to prevent gangrene.¹² It may be used in two ways for blood transfusions, i.e., by putting it in the flask into which the blood is to be drawn or by heparinizing the donor before withdrawal of the blood.

Heparin is administered intravenously in two ways: (1) the intermittent dose method and (2) the continuous drip method. In the intermittent dose method, a dose of 50 mgm. is repeated every four hours until a total of 250 mgm. per day have been given. The continuous drip method is to be preferred; it consists of a slow infusion of a heparin containing solution into the vein adjusting the flow according to the observed clotting time. A solution containing 100 to 200 mgm. of heparin in each 1,000 cc. of 5 per cent dextrose or physiologic saline solution is used for the latter method.

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24

Glycosides

GLYCOSIDES

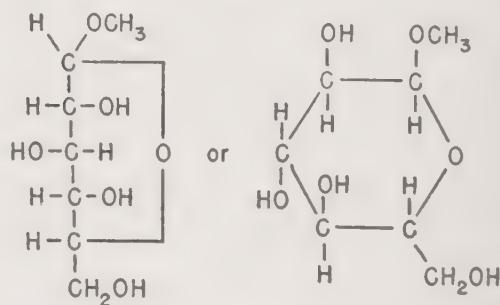
GLYCOSIDES

Because a number of plant constituents yielded glucose and an organic hydroxide upon hydrolysis, the term glucoside was introduced as a generic term for these substances. The fact that a number of plant constituents yielded sugars other than glucose led to the suggestion of the less specific general term glycoside. When the nature of the sugar residue is known, more specific terms can be used where desired, such as, glucoside, fructoside, rhamnoside, etc., respectively. The nonsugar portion of the glycoside is generally referred to as the aglycon or genin.

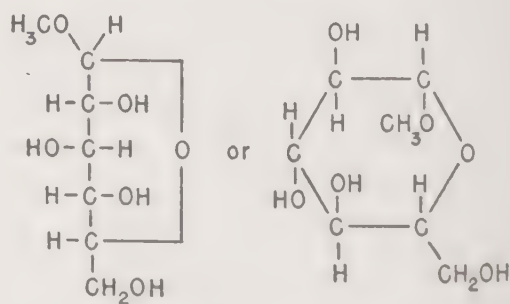
Two general types of glycosides are known, viz., the nitrogen glycosides and the conventional type glycoside. The conventional type glycoside has an acetal structure and can be illustrated by the simplest type in which methyl alcohol is the aglycon or organic hydroxide. Two forms of this simple and all other glycosides are possible, viz., alpha and beta, because of the asymmetry centering about carbon atom one of the sugar residue that contains the acetal structure. It is thought that all naturally occurring glycosides are of the beta variety because the enzyme emulsin, which cannot

CARDIAC GLYCOSIDES

hydrolyze synthetic alpha glycosides, hydrolyzes naturally occurring glycosides.



α -Methyl Glucoside



β -Methyl Glucoside

Some of the beta-glycosides are also hydrolyzed by amygdalase, cellobiase, gentiobiase and the phenol-glycosidases. The alpha glycosides are hydrolyzed by maltase, mannosidase and trehalase.

Glycosides are usually hydrolyzed by

acids and are relatively stable toward alkalis. Some glycosides are much more resistant to hydrolysis than others. For example, those glycosides that contain a 2-desoxy sugar (see cardiac glycosides) are easily cleaved by weak acids, even at room temperature. On the other hand, most of the glycosides containing the normal type of sugars are quite resistant to hydrolysis, and of these some may require rather drastic hydrolytic measures. The drastic treatment required for the hydrolysis of some glycosides causes chemical changes to take place in the aglycon portion of the molecule; these changes present problems in the elucidation of their structures. On the other hand, those glycosides that are very easily hydrolyzed present the problems of their isolation and storage. Examples of the latter are the cardiac glycosides.

The sugar component of glycosides may be a mono-, di-, tri- or tetrasaccharide. There is a wide variety of sugars found in the naturally occurring glycosides. Most of the unusual and rare sugars found in nature are components of glycosides.

The aglycons or nonsugar portions of glycosides are represented by a wide variety of organic compounds, as illustrated by Table 38 (page 374), the cardiac glycosides and saponins.

Because of the complexity of the structures of the naturally occurring glycosides, no generalizations are possible with regard to their stabilities if the stabilities of the glycosidic linkages are excluded. It also follows that considerable deviations are met with in their solubility properties. Many glycosides are soluble in water or hydroalcoholic solutions because the solubility properties of the sugar residues exert a considerable effect. Some glycosides, such as the phytosterolins and cardiac glycosides, are slightly soluble or insoluble in water. In these cases, the steroid aglycon is markedly insoluble in water and offsets the solubility properties of the sugar residues. Most glycosides are insoluble in ether. Some

glycosides are soluble in ethyl acetate, chloroform or acetone.

Glycosides occur widely distributed in nature. They are found in varying amounts in seeds, fruits, roots, bark and leaves. In some cases two or more glycosides are found in the same plant, e.g., cardiac glycosides and saponins. Glycosides are often accompanied by enzymes that are capable of synthesizing or hydrolyzing them. This phenomenon introduces problems in the isolation of glycosides because the disintegration of plant tissues, with no precautions to inhibit enzymatic activity, leads, in some cases, to partial or complete hydrolysis of the glycosides.

Most glycosides are bitter to the taste, although there are many that are not. Glycosides per se or their hydrolytic products furnish a number of drugs, some of which are very valuable. Some plants that contain the cyanogenetic type of glycoside present an agricultural problem. Cattle have been poisoned by eating plants which are rich in the cyanogenetic type of glycoside.

Salicin N.F. occurs in many species of *Salix* and *Populus* in amounts as high as 7.5 per cent. "Salicin occurs as colorless, silky, shining needles or prisms, or as a white crystalline powder. It is odorless, and has a very bitter taste. One Gm. of Salicin dissolves in about 25 cc. of water and in about 90 cc. of alcohol, at 25°."

Salicin, because it yields glucose and salicyl alcohol (saligenin) upon hydrolysis, had some value as an antipyretic and analgesic.

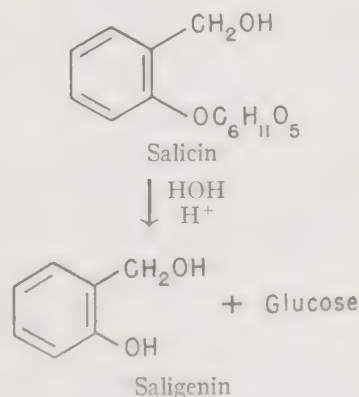
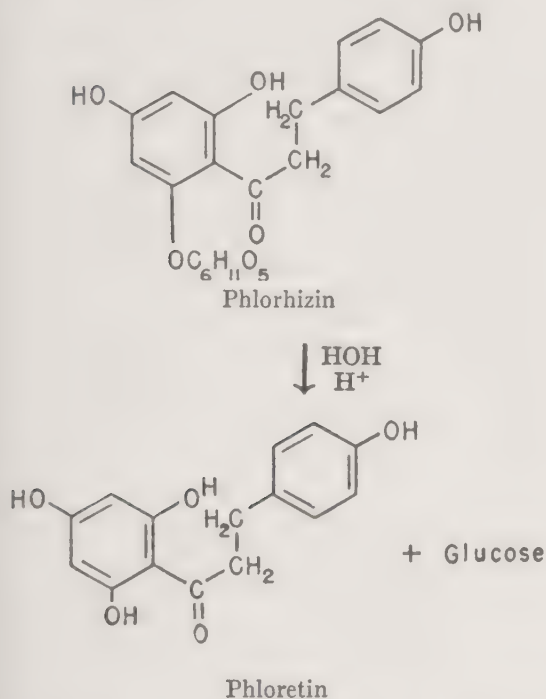


TABLE 38. BOTANICAL SOURCES, AGLYCONS AND SUGAR COMPONENTS
OF A NUMBER OF GLYCOSIDES

GLYCOSIDE	BOTANICAL SOURCE	AGLYCON	SUGAR
Arbutin	<i>Arbutus uva ursi</i>	Hydroquinone	Glucose
Methyl arbutin	<i>Pyrus communis</i>	Methyl hydroquinone	Glucose
Gein	<i>Geum urbanum</i>	Eugenol	
Coniferin	Conifers	Coniferyl alcohol	Glucose
Populin	<i>Populus</i> sp.	Saligenin	Benzoyl glucose
Salicin	<i>Salix</i> sp.	Saligenin	Glucose
Syringin	<i>Syringia vulgaris</i>	5-Methoxy coniferyl alcohol	Glucose
Amygdalin	<i>Prunus Amygdalus</i>	Benzaldehyde and HCN	2-Glucose
Dhuirin	<i>Sorghum vulgare</i>	<i>p</i> -Hydroxybenzaldehyde and HCN	Glucose
Prunasin	<i>Prunus padus</i>	Benzaldehyde and HCN	Glucose
Spiraein	<i>Spireae kamtschatica</i>	Salicylic aldehyde	Glucose
Gaultherin	<i>Gaultheria procumbens</i>	Methyl salicylate	Primeverose
Picein	<i>Salix discolor</i>	<i>p</i> -Hydroxyacetophenone	Glucose
Phloridzin	<i>Prunus</i> sp.	Phloretin	Glucose
Glycyphillin	<i>Smilax glycyphylla</i>	Phloretin	Rhamnose
Ruberythric acid	<i>Rubia tinctorium</i>	1:2 Dihydroxy anthranquinone (Alizarin)	1-Glucose
	<i>Olenlandia umbellata</i>		1-Xylose
Purpurin glycoside	<i>Rubia tinctorium</i>	1:2:4 Trihydroxyanthraquinone (Purpurin)	1-Glucose
Rubiadin glycoside	<i>Rubia tinctorium</i>	1:3 Dihydroxy-2-methyl anthraquinone (Rubiadin)	1-Glucose
Xanthopurpurin	<i>Rubia tinctorium</i>	1:3 Dihydroxy anthraquinone	1-Glucose
Frangulin	<i>Rhamnus frangula</i> <i>Cascara sagrada</i> <i>Rhamnus Purshranus</i> <i>Rheum</i> Buckthorn bark	4:5:7-Trihydroxy-2-methylanthraquinone (Frangula-emodin)	1-Rhamnose
Morindin glycoside	<i>Morinda citrifolia</i> , <i>M. umbellata</i>	Morindone (1:5:6-Trihydroxy-2-methyl-anthraquinone)	2-Glucose
Munjistin glycoside	<i>Rubia munjista tinctorium</i> <i>R. siccimensis</i>	1:3-Dihydroxy-2-carboxy anthraquinone	1-Glucose
Barbaloin or Aloin glycosides	<i>Aloe spicata</i> , <i>A. arborescenz</i> , <i>A. socotrina</i> , etc.	Aloe-emodin, (4:5-dihydroxy-2-hydroxy methyl-anthraquinone)	Arabinose
Chrysophanein	Chinese Rhubarb	Chrysophanic Acid (4,5-dihydroxy-2-methyl-anthraquinone)	Glucose
Rubiadin glycoside	<i>Lalium verum</i>	Rubiadin	Primverose
Melilotin	<i>Melilotus altissima</i>	Coumarin	Glucose
Skimmin	<i>Skimmia japonica</i>	7-Hydroxy coumarin (Umbelliferon)	Glucose
Aesculin	<i>Aesculus hippocastanum</i>	6-7-Dihydroxy coumarin (Aesculetin)	Glucose
Scopolin	<i>Atropa belladonna</i>	6-Methoxy-7-Oxycoumarin (Scopoletin)	2-Glucose
Daphnin	<i>Gnida polycephala</i>	7-8-Dihydroxycoumarin (Daphnetin)	Glucose
Fraxin	<i>Fraxinus Ornus</i>	6-Methoxy-7-8-dihydroxy-coumarin (Fraxetin)	Glucose
Sinigrin	<i>Brassica nigra</i> <i>Sinapis nigra</i>	$\text{CH}_2=\text{CHCH}_2-\text{N}=\text{C}=\text{S}+\text{KHSO}_4$ Allyl isothiocyanate	Glucose
Sinalbin	<i>Brassica alba</i>	4-Hydroxy-3:5-dimethoxy cinnamic acid choline ester (Sinapin), <i>p</i> -hydroxy-benzylisothiocyanate	Glucose
Gluconapin	<i>Brassica rapus</i>	$\text{CH}_3\text{C}=\text{C}-\text{CH}_2-\text{N}=\text{C}=\text{S}$ H H H H Crotonyl isothiocyanate	Glucose
Glucocheiralin	Wall flower seeds	$\text{CH}_3\cdot\text{SO}_2(\text{CH}_2)_3-\text{N}=\text{C}=\text{S}+\text{KHSO}_4$	Glucose
Erysolin	<i>Erepimum perouskianum</i>	$\text{CH}_3\text{SO}_2(\text{CH}_2)_4-\text{N}=\text{C}=\text{S}+\text{KHSO}_4$	Glucose

The average dose is 1 Gm.

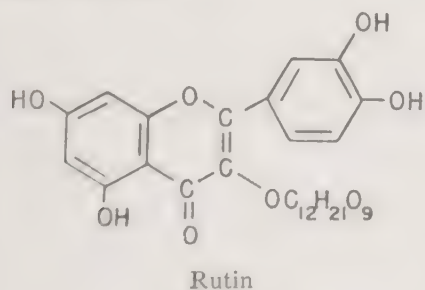
Phlorhizin (Phlorizin) is a glucoside obtained from the root of the apple, pear, cherry, etc. Upon hydrolysis it yields glucose and the dihydrochalcone, phloretin.



Phlorizin occurs as a white or yellowish crystalline powder that is sparingly soluble in water and soluble (1:4) in alcohol.

When administered to man or animals, phlorhizin produces glycosuria of renal origin. When administered by injection, it is used as a means of testing the functional activity of the kidney.

Rutin is a rhamno-glycoside of the flavonol, quercetin, and has been assigned¹ the following formula.

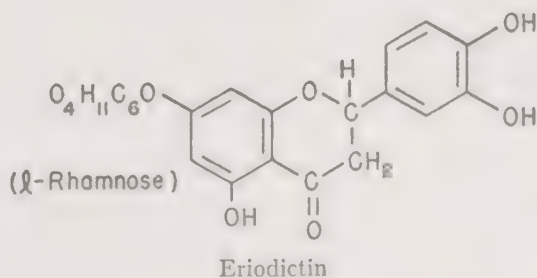
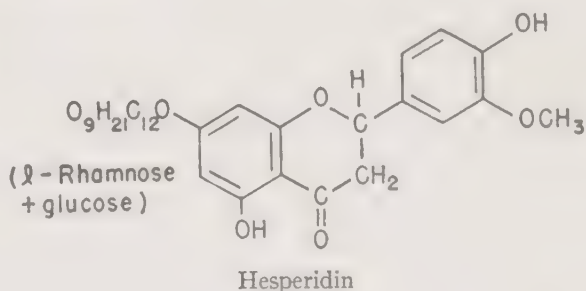


Rutin occurs in varying concentrations in yellow pansies, fresh forsythia flowers² (1 to 4 per cent), hydrangea, garden rue, violets,

elder flowers, bright tobacco leaves (0.4 per cent), and green buckwheat³ (3.2 to 8 per cent). Rutin is found only in flue-cured tobacco leaves and the best yields are obtained from leaves of high quality U. S. Grade C3L or better. Because of its high content, green buckwheat furnished the best commercial source of supply of rutin.

Rutin occurs as yellow, needle-shaped crystals that are difficultly soluble in water (0.15 Gm. per liter at 20° C.) soluble in alcohol, acetone or ethyl acetate and insoluble in chloroform, ether or the hydrocarbons. Because rutin contains a catechol group, it is unstable to light, oxidizing agents and alkalis or alkali bicarbonates.

Szent-Gyorgyi *et al.*⁴ reported in 1936 that lemon juice or extracts of Hungarian red pepper were beneficial in a number of cases of purpura hemorrhagica which had failed to respond to large doses of ascorbic acid. Because a factor other than ascorbic acid was thought to be responsible for this activity, it was given the name vitamin P, to indicate its effect on the permeability of the capillaries. A crystalline flavanone glycoside fraction called "citrin" was isolated from lemon juice and shown to be physiologically active. "Citrin" was subsequently shown to contain largely hesperidin together with smaller amounts of eriodictyol glycoside (eriodictin).⁵

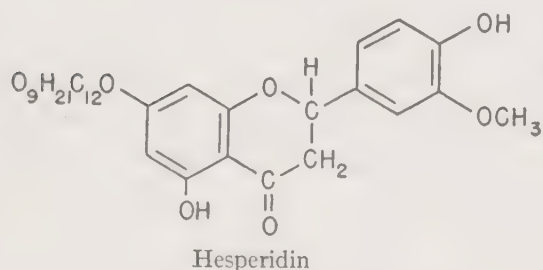


As a result of chromatographic studies of citrin, Robeziels⁶ detected the presence of a third pigment that had quercitrinlike properties. This discovery may explain the observation that citrin brings about a definite lowering of blood pressure.⁷ Therefore, sources of rutin, a well-known flavonol glycoside, were sought in order to test it for its activity.

Preliminary clinical data indicate that rutin may favorably decrease capillary fragility in a high percentage of cases, when it is administered over a period of many weeks or months. Increased capillary fragility may be encountered in patients with hypertension, diabetes mellitus, hereditary telangiectasia, and as a complication of salicylate, thiocyanate and arsenical therapy. Rutin appears to be of value in certain cases of glaucoma by decreasing intraocular pressure when it is used with miotics.

The recommended dosage of rutin is one or two 20 mg. tablets three or four times daily.

Hesperidin Methyl Chalcone. Investiga-



tions upon pure substances⁸ indicated that the hesperidin and eriodictyol⁹ of "citrin" did not have the pronounced effect on capillary permeability as originally reported for "citrin." On the other hand, the water-soluble, yellow pigment from crude orange hesperidin was found to increase capillary permeability in certain individuals whose capillary permeability was below normal. This compound was shown to be hesperidin chalcone.

Hesperidin chalcone, like other chalcones containing a phloroglucinol ring, readily is converted to flavones in acid solution, when

heated or upon prolonged standing in the dry state. Conversely, flavones are converted to chalcones by the action of alkali. Methylation of one of the phenolic groups in the phloroglucinol portion of the chalcones stabilizes or prevents ring closure to form the flavones.

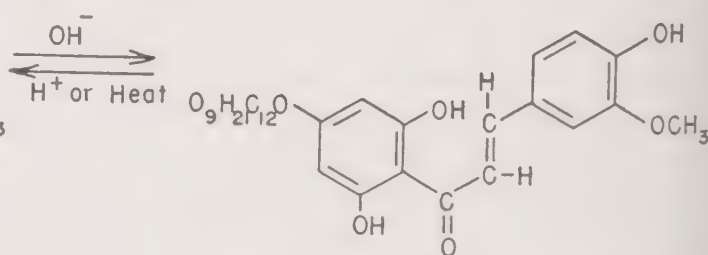
The stabilized hesperidin methyl chalcone has lost none of the capillary permeability properties shown to be present in hesperidin chalcone.

Hesperidin methyl chalcone is a deep yellow powder which is readily soluble in water, quite soluble in alcohol and acetone and slightly soluble in ether.

Parenteral administration of hesperidin methyl chalcone causes a striking depression of blood pressure. Orally it is claimed to increase capillary permeability. (Vitamin P? activity.) For uses see rutin.

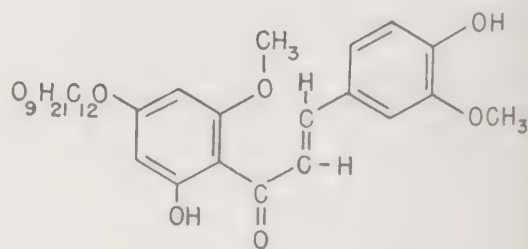
Hesperidin methyl chalcone is sold in 50 mg. capsules.

Good sources of substances that appear to restore abnormally increased permeability of capillaries are grapes, lemons, oranges,



Hesperidin Chalcone

↓ Methylation



Hesperidin Methyl Chalcone

rose hips, blue plums, prunes and black currants. Moderately good sources are grapefruit, apricots, cherries, blackberries and

blueberries. Little or no activity was found in tomatoes, cabbage, cauliflower, lettuce, turnips, carrots, potatoes and parsnip. Although some of the above sources contain much vitamin C, there is no constant relationship between the vitamin C content and vitamin P? activity.¹⁰ This is particularly true of grapes.

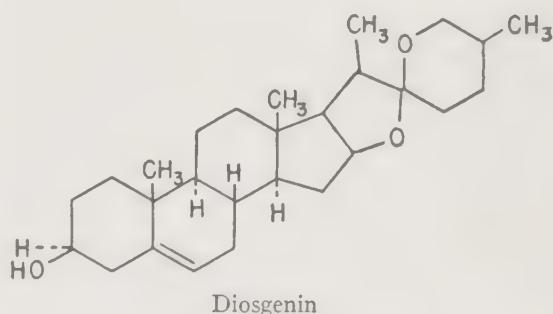
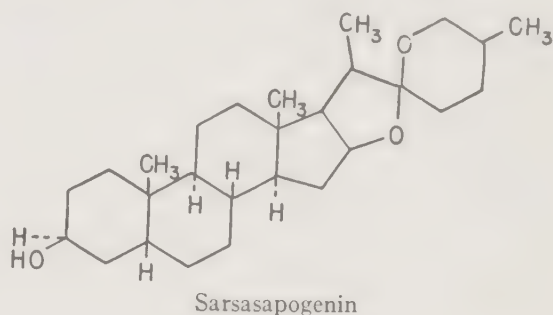
Saponins are glycosides that are found in plants and have the property of forming colloidal aqueous solutions which foam upon shaking. Like glycosides, saponins vary in chemical structure. Most saponins, even in high dilution, are able to effect hemolysis of red blood cells. In this respect they are very toxic to cold blooded animals. In general, they have a bitter taste and are extremely irritating to the eyes and nose. The more commonly and abundantly occurring saponins are those found in soapbark, soap root, snake root, smilax, cacti and many plants that grow in the desert regions of the southwestern U. S. and in Mexico. Many saponins occur as admixtures and, because some of these are so closely related in physical properties, they are very difficult to separate from one another. Therefore, in a number of instances the crude mixtures are hydrolyzed to facilitate the separation and study of the aglycons.

The digitalis saponins form solid molecular complexes with the higher alcohols, phenols and thiophenols. Digitonin has proven particularly useful in the field of steroidal chemistry, where it forms insoluble complexes, that are readily isolated, with those steroids that have a C_3 -OH that is normal. Those in which the C_3 -OH is epi form complexes that are soluble. Thus, a twofold usefulness is gained, i. e., determination of the configuration about C_3 -OH and a means of purification, because these complexes can readily be resolved into their respective components.

Sarsasapogenin, whose structure and chemistry have been intensively investigated, is one of a large number of sapogenins whose structures are very closely related.

These sapogenins have proved exceedingly useful as starting materials for the synthesis of testosterone, progesterone and desoxycorticosterone.

Examples of these types of sapogenins can be illustrated by sarsasapogenin and diosgenin.



Sapogenins which yield sapotalene upon dehydrogenation with selenium are thought to be triterpene oxygenated compounds that contain 30 carbon atoms. Some of these genins (aglycons) are glycyrrhetic acid, hederagenin, aescigenin, quillaigenin and cyclamiertine.

Table 39 gives a number of steroidal saponins together with their aglycons and sugar components.

Some of the aglycons shown exist in glycosidal combination and are found in other plants. The following aglycons have structures that are closely related to those given above: smilagenin, chlorogenin, neotigogenin, liligenin, nitogenin, hecogenin, manogenin, yuccagenin, kammogenin, rockogenin, agavogenin, furocogenin, samogenin, mexagenin, yamegenin, texegenin, kryptogenin, kammogenin and nologenin.

TABLE 39. BOTANICAL SOURCES, AGLYCONS, FORMULAE AND SUGAR COMPONENTS OF A NUMBER OF SAPONINS

SAPONIN	BOTANICAL SOURCE	AGLYCON	FORMULA	SUGAR
Digitonin	<i>Digitalis purpurea</i>	Digitogenin	$C_{27}H_{44}O_5$	4-Galactose xylose
Gitonin	<i>Digitalis purpurea</i>	Gitogenin	$C_{27}H_{44}O_4$	3-Galactose pentose
Tigonin	<i>Digitalis lanata</i>	Tigogenin	$C_{27}H_{44}O_3$	2-Glucose 2-Galactose Rhamnose
Sarsasaponin	<i>Radix sarsapillae</i>	Sarsasapogenin	$C_{27}H_{44}O_3$	3-Glucose Rhamnose
Amolonin	<i>Chlorogalum pomeridianum</i>	Tigogenin	$C_{27}H_{44}O_3$	3-Glucose 2-Rhamnose Galactose
Trillin	<i>Trillium erectum</i>	Diosgenin	$C_{27}H_{42}O_3$	Glucose

CARDIAC GLYCOSIDES

William Withering, in 1785, published a treatise entitled *An Account of the Foxglove and Some of Its Medical Uses*. Since that time there has been a gradual increase in the use of digitalislike substances. A rather large number of naturally occurring substances are closely related in structure and activity to the active compounds of foxglove, i. e., digitalis. These compounds, because of their glycoside structures and cardiac action, are often called the cardiac glycosides or heart poisons. They are characterized by the highly specific and powerful action which they exert upon the cardiac muscles. In the proper dosage, many of them are very valuable in the treatment of heart disease. They stimulate the heart to greater contractile activity. In addition, they have an irritant and diuretic action.

These active glycosides are found in a number of plant families such as *Apocyanaceae*, *Scrophulariaceae*, *Liliaceae* and *Ranunculaceae*. Some of the so-called African arrow poisons are prepared from the *Strophanthus* species, *Apocynum cannabinum*, *Periploca graeca*, *Gomphocarpus*, etc. The sea onion or squill, *Scillia maritima*, has also proven a useful drug. Squill is one of the oldest drugs used in medicine. Squill was used in ancient times by the Egyptians,

Greeks and Romans for the treatment of many illnesses, and they worshiped the plant as a general protector against evil. The earliest mention of squill is found in a medical prescription contained in the Papyrus Ebers (about 1500 B. C.). G. L. B. van Swieten, in 1764, emphasized the importance of squill as a remedy against dropsy and used, with clear insight, fresh squill because he found it to be especially active. However, Withering's introduction of the foxglove as a cardiac remedy resulted in the disuse of squill, even though F. Home, in 1780, discovered that squill was cardio-active. Nevertheless, squill and its preparations were always mentioned in pharmaceutical textbooks.

The physiologic potency of the cardiac glycosides and tinctures of the drugs that contain them is determined experimentally by injecting an aqueous alcoholic solution of the glycoside into the blood stream of cats or in the lymph sac of frogs. The smallest dose or amount of the substance necessary to produce systolic standstill of the heart is determined, and the so called minimum lethal dose (M. L. D.) is calculated per kilogram of cat or per gram of frog. The cat assay is official in the U.S.P. and is thought to give more uniform results and, therefore, permit the preparation of more uniform cardiac active products. Some spe-

cimens of digitalis leaf or tinctures, however, when tested against the standard by oral administration in man and intravenous injection in the cat, give different results. In some cases, samples of digitalis having a potency of 1 U.S.P. unit by the cat method produce an effect three times greater when given orally to man. One reason for the discrepancy is that the intravenous method does not distinguish between absorbable and non-absorbable materials. A preparation may be potent by vein and weak by mouth if it is not well-absorbed. It is reported that discrepancies between the cat and human methods of assay are even greater in the case of the purified glycosides. The unit of one material may produce a therapeutic effect 10 times as great as a unit of another substance.

It is important that a digitalis preparation be well-absorbed because those glycosides that are easily desugared in vitro or are poorly or irregularly absorbed, thereby disturbing the smooth course of digitalization, are not so satisfactory because larger doses are required to produce systemic effects. Outstanding examples are strophanthin and ouabain, although some other preparations are not as desirable as they could be. Only about one-fifth of a dose of digitalis leaf or tincture, given by mouth, is absorbed. The remaining four-fifths contributes nothing to therapeutic effect but adds to local irritant action. The ratio between oral and intravenous dose is one way to determine absorption of a preparation, for example, digitoxin is 1:1, therefore, complete absorption; digitofoline is 5:1, therefore, one-fifth of the dose is absorbed; lanatosid C is 10:1, therefore, one-tenth of the dose is absorbed.

Another factor of importance is the time required for a material to develop its full effect. All of the effects likely to occur from a single injection of ouabain or crystalline strophanthin take place within two hours. A single injection of digitoxin develops its full effect in about six hours. Digitofoline and lanatoside C stand between two and six

hours. Therefore, ouabain is the drug of choice in an emergency for an immediate effect. Also, it follows that digitoxin dosage by intravenous injection need not be repeated in less than four or five hour intervals. The duration of action of digitoxin is greater than that of ouabain; i. e., two-thirds of the effect of ouabain wears off in four days whereas less than one-third of the effect of digitoxin wears off in the same length of time.¹¹

Cardiac activity is not entirely limited to the glycosides, for some of the *Erythrophloeum* alkaloids and the bufagins and bufotoxins of the toads exhibit the same type of activity.¹²

Table 40 (pages 380 and 381) gives a number of cardiac glycosides together with their botanical sources and hydrolytic products.

Table 41 (see page 382)¹³ gives the M.L.D. in cats and the M.S.D. in frogs of a number of naturally occurring cardiac glycosides, some synthetic glycosides and their acetates, strophanthin and its acetate, a few other aglycons together with one alkaloid erythrophlein sulfate and one toad poison (bufotalin).

Most of the physiologic activity of the cardiac glycosides resides in the aglycon portion of the molecule. With the exception of the squill glycosides and helebrin from *Radix Hellebori nigri*, the cardiac glycosides are substituted etiocholanyl-butenolides or 21-hydroxy-norcholenic acid lactones and etioallocholanyl-butenolides or 21-hydroxy norallocholenic acid lactones. The type and extent of substitution, together with certain stereochemical configurations in the aglycons,¹⁴ determines very markedly the degree of activity in the cardiac glycosides. For example, the aglycons, digitoxigenin, thevetigenin and uzarigenin, differ only from each other in certain stereochemical aspects which can be depicted as is shown on page 383.

Digitoxigenin is more active than thevetigenin, and these two differ only in that the C₃OH of the former is trans to the methyl

TABLE 40. BOTANICAL SOURCES, FORMULAS, MELTING POINTS, AGLYCONS AND SUGAR COMPONENTS OF A NUMBER OF CARDIAC GLYCOSIDES

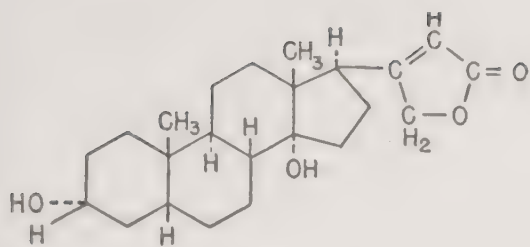
GLYCOSIDE	BOTANICAL SOURCE	FORMULA	M.P.	AGLYCON	FORMULA	M.P.	SUGAR COMPONENTS
Digitoxin	<i>Digitalis purpurea</i> (leaves)	$C_{41}H_{64}O_{13}$	263	Digitoxigenin	$C_{23}H_{34}O_4$	250	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Digilanide-A or Lanatosid-A Purpurea	<i>D. lanata</i>	$C_{49}H_{76}O_{19}$	248	Digitoxigenin	$C_{23}H_{34}O_4$	250	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Glycoside-A	<i>D. purpurea</i>	$C_{47}H_{74}O_{18}$	225	Digitoxigenin	$C_{23}H_{34}O_4$	250	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Gitoxin	<i>D. purpurea</i>	$C_{41}H_{64}O_{14}$	285	Gitoxigenin	$C_{23}H_{34}O_5$	232	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Digilanide-B or Lanatosid-B Purpurea	<i>D. lanata</i>	$C_{49}H_{76}O_{20}$	248 238	Gitoxigenin	$C_{23}H_{34}O_5$	...	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Glycoside-B	<i>D. purpurea</i>	$C_{47}H_{74}O_{19}$	240	Gitoxigenin	$C_{23}H_{34}O_5$	...	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Digoxin	<i>D. lanata</i>	$C_{41}H_{64}O_{14}$	265	Digoxigenin	$C_{23}H_{34}O_5$	220	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Digilanide-C or Lanatosid-C Diginin	<i>D. lanata</i>	$C_{49}H_{76}O_{20}$ $C_{28}H_{40}O_7$	248	Digoxigenin Diginigenin (Dianhydre- gitoxigenin)	$C_{23}H_{34}O_5$ $C_{21}H_{28}O_4$	...	3-Digitoxose 3-Digitoxose 1-Glucose 1-Acetic Acid 3-Digitoxose 1-Glucose
Digitalin	<i>D. purpurea</i> (seeds)	$C_{36}H_{56}O_{14}$	229 138	Digitaligenin	$C_{24}H_{32}O_3$	211	Digitalose Glucose
Cymarine	<i>Apocynum cannabinum</i> ; <i>A. venetum</i> ; <i>A. androsaemii</i> - <i>volium</i> (seeds)	$C_{30}H_{44}O_9$	148	Strophanthidin	$C_{23}H_{32}O_6$	171	Cymarose
K-Strophanthin-β	<i>Strophanthus Kombe</i>	$C_{36}H_{54}O_{14}$	187	Strophanthidin			Cymarose Glucose
K-Strophanthoside	<i>Strophanthus Kombe</i>			Strophanthidin			Cymarose 2-Glucose
Ouabain	<i>Acocanthera</i> Sp. (bark and root)	$C_{29}H_{44}O_{12}$	188	Ouabagenin	$C_{23}H_{34}O_8$	...	Rhamnose
(g-Strophanthin)	<i>Strophanthus gratus</i> (seed)						

TABLE 40 (CONTINUED)

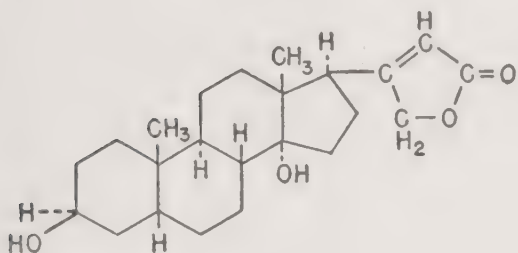
GLYCOSIDE	BOTANICAL SOURCE	FORMULA	M.P.	AGLYCON	FORMULA	M.P.	SUGAR COMPONENTS
Scillaren-A	<i>Scilla maritima</i> (Bulb)	$C_{37}H_{54}O_{13}$	270	Scillaridin A	$C_{25}H_{32}O_3$	245-250	Rhamnose, Glucose
Proscillaridin-A	<i>S. maritima</i>	$C_{31}H_{44}O_8$	213	Scillaridin A	$C_{25}H_{32}O_3$	245-	
Oleandrin	<i>Nerium oleander</i>	$C_{32}H_{48}O_9$	249	Oleandrigenin	$C_{25}H_{36}O_6$	250	Rhamnose
				Dianhydro-		223	Oleandrose
Oridigin		$C_{35}H_{54}O_{13}$	...	gitoxygenin	$C_{23}H_{32}O_6$	213	Glucose, 2,6-Desoxy hexose
				Dianhydro-			
α -Antiarin	<i>Antiaris toxicaria</i>	$C_{29}H_{42}O_{11}$	...	antiarigenin	$C_{23}H_{28}O_5$	167	Antiarose
β -Antiarin	<i>A. toxicaria</i>	$C_{29}H_{42}O_{11}$	...	Dianhydro-antiarigenin	$C_{23}H_{28}O_5$	167	Rhamnose
Calotropin	<i>Calotropis procera</i>	$C_{29}H_{40}O_9$	...	Anhydro-calotropagenin	$C_{23}H_{32}O_6$	221	Methyl Reductic Acid
Calotoxin	<i>C. gigantea</i>	$C_{29}H_{40}O_{10}$	...	Anhydro-calotropagenin	$C_{23}H_{32}O_6$	242	Hydroxy Methyl Reductic Acid
Uzarin	<i>Gomphocarpus</i>	$C_{35}H_{54}O_{14}$	268-	Uzaringenin	$C_{23}H_{34}O_4$	247	2-Glucose
Periplocymarin	<i>Periploca graeca</i>	$C_{29}H_{44}O_9$	270	Anhydro-uzaringenin	$C_{23}H_{34}O_5$	168	Cymarose
Periplocin	<i>P. graeca</i>	$C_{36}H_{56}O_{13}$	138	Periplogenin			Cymarose & Glucose
			224	Periplogenin			
Sarmentocymarin	<i>Strophanthus</i>						
	<i>Sarmentosus</i>	$C_{30}H_{46}O_8$	130	Sarmentogenin	$C_{23}H_{34}O_5$	270	Sarmentose
Thevetin	<i>Thevetia nerifolia</i> ,			Thevetigenin	$C_{23}H_{34}O_4$	218	Digitulose
Convallatoxin	<i>T. ycotili</i>	$C_{42}H_{66}O_{18}$	195	Anhydro Thevetigenin	$C_{23}H_{32}O_3$	...	2-Glucose
	<i>Convallaria</i>			Dianhydro-			
	<i>Majalis</i> (flowers)	$C_{30}H_{44}O_{10}$	...	Convallitoxigenin	$C_{24}H_{30}O_4$	...	Rhamnose
				Anhydro-			
Cerberin	<i>Cerbera odallam</i>	$C_{29}H_{44}O_8$	191-193	Cerberigenin	$C_{23}H_{32}O_3$	...	Cerberose
Adynerin		$C_{30}H_{44}O_7$	...	Adynerigenin	$C_{23}H_{32}O_4$	242	Oleandrose

TABLE 41. M.L.D. IN CATS AND M.S.D. IN FROGS OF A NUMBER OF COMPOUNDS

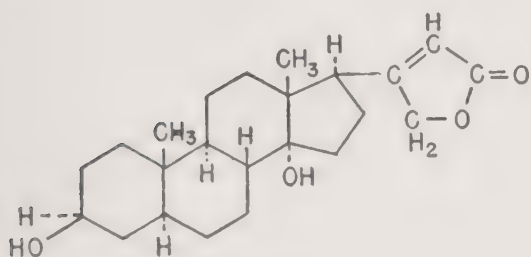
COMPOUND	ASSAY IN CATS			ASSAY IN FROGS
	M. L. D.			MEAN SYSTOLIC DOSE
	$\pm$ STANDARD ERROR			$\mu\text{g.}/\text{GM. FROG}$
			$\mu\text{g.}/\text{Kg. Cat}$	
Convallatoxin	80	$\pm$	2	0.21
β -Antiarrin	100	$\pm$	4	0.39
Ouabain	120	$\pm$	2	0.50 to 0.82 $\pm$ 0.02
Calotropin	120	$\pm$	2	0.50
Cymarin	130	$\pm$	3	0.60 $\pm$ 0.006
α -Antiarrin	130	$\pm$	3	0.50
Scillaren A	150	$\pm$	7	0.70
Emicymarin	170	$\pm$	10	2.05
Folierin	200	$\pm$	8	1.27
Sarmentocymarin	210	$\pm$	8	5.45
Digoxin	220	$\pm$	8	2.50
Digitoxin	330	$\pm$	8	8.00
Thevetin	920	$\pm$	35	4.50
Periplocymarin	151	$\pm$	4	3.18
Desacetyloleandrin	308	$\pm$	16	11.67
Uzarin	5080	$\pm$	437	1500
Strophanthidin	306.2	$\pm$	38.7	2.71 $\pm$ 0.49
Strophanthidin Acetate	186.6	$\pm$	24.6	2.19 $\pm$ 0.13
Strophanthidin- β - <i>D</i> -Glucoside	91.3	$\pm$	2.46	0.583 $\pm$ 0.04
“ β -tetraacetyl- <i>D</i> -glucoside	1166	$\pm$	125	18.77 $\pm$ 3.07
“ β - <i>D</i> -Xyloside	10.95	$\pm$	4.39	0.64 $\pm$ 0.04
“ β -triacetyl- <i>D</i> -xyloside	591.6	$\pm$	70.4	8.07 $\pm$ 1.35
“ β - <i>L</i> -arabinoside	94.5	$\pm$	2.95	0.308 $\pm$ 0.03
“ β -triacetyl- <i>L</i> -arabinoside	1230	$\pm$	136.6	6.33 $\pm$ 0.38
“ β -tetraacetyl- <i>D</i> -galactoside ...	1692	$\pm$	168	11.29 $\pm$ 1.85
Erythrophlein sulphate	370	$\pm$	17	
Bufotalin [.....	130	$\pm$	6	
Digitoxigenin	459.1	$\pm$	36.3	61.93 $\pm$ 4.63
Digitoxigenin- β - <i>D</i> -glucoside	124.7	$\pm$	11.86	3.9 $\pm$ 0.457
Digitoxigenin- β -tetraacetyl- <i>D</i> -glucoside	1184	$\pm$	127.1	117.5 $\pm$ 69.4
Digoxigenin	441.5	$\pm$	42	33.13 $\pm$ 2.52
Digoxigenin- β - <i>D</i> -glucoside	100.3	$\pm$	5.0	2.26 $\pm$ 0.256
Digoxigenin- β -tetraacetyl- <i>D</i> -glucoside	1057	$\pm$	146.9	9.53 $\pm$ 0.404
Periplogenin	719.3	$\pm$	81.3	85.82 $\pm$ 8.06
Periplogenin- β - <i>D</i> -glucoside	118.8	$\pm$	5.79	22.07 $\pm$ 2.097
Periplogenin- β -tetraacetyl- <i>D</i> -glucoside	2599	$\pm$	178	



Digitoxigenin



Thevetigenin



Uzarigenin

group at C_{10} , whereas in the latter this relationship is *cis*. When the $C_3\text{OH}$ is *cis* it is called *alpha* or *epi* and when it is *trans* it is called *beta* or *normal*. All very active cardiac glycosides have an *alpha* OH at C_3 . Uzarigenin has a very much weaker heart action than thevetigenin, and these two differ from each other only in that rings A and B of the former are *trans* to each other, whereas in the latter they are *cis*. In steroids, when rings A and B are *cis* they belong to the normal series, whereas when they are *trans*, they usually are referred to as *allo*. All very active cardiac glycosides have a *cis* fusion of rings A and B. The OH at C_{14} is necessary for activity because synthetic models, for example, 3(α)-hydroxy-etiocholan-1-yl-butenolide are inactive. The double bond¹⁵ in the lactone side chain is necessary for marked activity because reduction of the double bond of this ring in cymarins reduces

its activity to one-twenty-third of its original value. Dihydroouabain is one-sixteenth as active as ouabain. Enzymatic activity can alter the stereochemistry of the hydrogen and side chain at C_{17} with the resultant formation of *allo* compounds which are inactive. This enzymatic change (Walden inversion) may account for some of the loss in activity encountered in these drugs. Under certain conditions, the double bond in the side chain can shift to the β - γ position and react with the $C_{14}\text{—OH}$ to form a new ring containing an oxygen bridge to give the *iso* compounds which are inactive physiologically. The replacement of the $C_{10}\text{—CH}_3$ group by an aldehyde or primary alcohol group increases the activity as they are found in the most active cardiac glycosides, such as ouabain, strophanthin and convallatoxin. This may not be a logical conclusion because these glycosides contain less sugar than digitoxin (for example). Reference to Table 41 shows that the synthetic glycosides that contain a monosaccharide have approximately equal activity.

The partial or complete elimination¹⁶ of the sugar at $C_3\text{—OH}$ from the glycosides originally present in the drug brings about a less pronounced decrease in the therapeutic activity. It has been observed, especially with the glycosides of squill and digitalis, that, as a rule, a lower sugar-component content will indicate a lower solubility of the compound in water. Decreased solubility may be responsible for poor absorption in the intestinal tract, and hence it is understandable that the activity of an extract decreases as the sugar content of the glycoside is reduced. The diglanides¹⁷ (total glycosides of *Digitalis lanata*) are about one-third again as active as digitoxin. An infusion of digitalis contains only one-half the glycosides as the natural glycosides. Synthetic studies have shown that when the sugar moiety is composed of a monosaccharide, the nature of the sugar is not very significant in so far as its effect on the activity is concerned.

It is interesting to note that a C₃—OAc in strophanthidin acetate gives a more active compound than strophanthidin itself.

Under proper storage conditions the cardiac glycosides are stable over long periods of time whether they be in a purified form or in the original powdered leaf. A freshly prepared tincture probably contains large amounts of "genuine glycosides." By this term is meant the unchanged, initial cardiac glycosides as they pre-exist in the fresh plant, carefully dried. Comparative standardization of tinctures of known age by both the cat and frog methods shows a rapid decrease in the apparent toxicity (activity) as determined by the frog method, without a corresponding decrease as determined by the cat method. This indicates some change that affects the absorption of the original active glycosides. Because digitoxin is slowly and irregularly absorbed from the frog lymph sac, it is thought some of the genuine glycosides may be partially desugared in the tincture upon standing, to give less absorbable (from frog lymph sacs) substances.

Some of these cardioactive glycosides, such as strophanthin and those obtained from digitalis, have a 2-deoxy sugar directly linked to the C_3 —OH. These 2-deoxy sugars are very easily cleaved by even weak hydrogen ion concentrations.¹⁸ However, the glucose residue in the genuine glycosides of digitalis is cleaved more readily. The sugar residues in such glycosides as ouabain and convallatoxin are fairly resistant to hydrolysis.

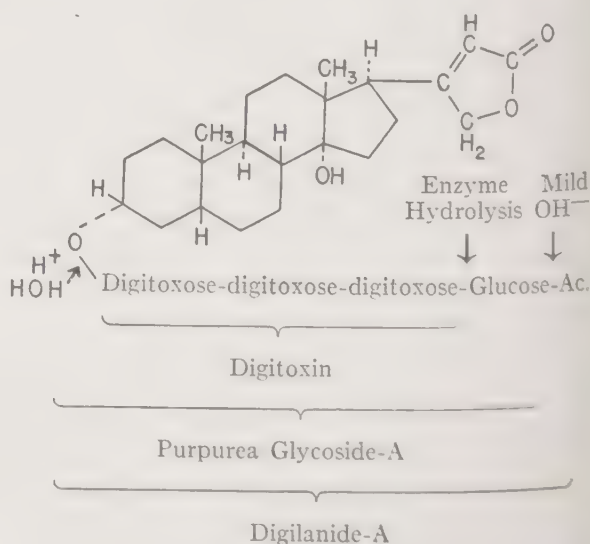
The side chain at C₁₇ can be isomerized by enzymatic means to give the allo compounds, which are inactive.¹⁹ The side chain, because of its lactone character, can be saponified by alkali. Because this side chain is an α - β -butenolide, it gives an aldehydic acid upon alkaline saponification and thus gives a positive Legal's test. The side chain plays a role in the Baljet and Raymond reactions, which have been used as

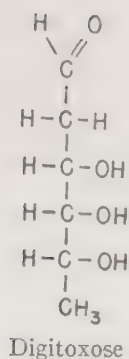
bases for quantitative colorimetric procedures.²⁰

The U.S.P. color test for digitoxin is essentially the Keller-Kiliani test. The concentrated sulfuric acid layer becomes red brown to violet brown (aglycons) and the acetic acid layer becomes blue (digitoxose).

The trend in cardiac therapy is toward the increased use of single purified cardiac glycosides or purified mixtures of these glycosides. This is done in order to standardize more accurately the product or drug and the treatment of the patient.

Digitoxin U.S.P. "is either pure digitoxin ($C_{41}H_{64}O_{13}$) or a mixture of cardioactive glycosides obtained from *Digitalis purpurea* Linné (Fam. *Scrophulariaceae*) and consisting chiefly of digitoxin." Digitoxin was first described as a pure or nearly pure crystalline substance "digitaline crystallisee" in 1869 by Nativelle.²¹ However, the careful chemical and pharmacological investigation of digitoxin was not published until 1920 by Cloetta.²² Digitoxin per se pre-exists in *Digitalis purpurea* as purpurea glycoside A²³ and differs from the latter in that the sugar moiety has lost a molecule of glucose by hydrolysis. It also pre-exists in *Digitalis lanata* as digilanide A or lanatosid-A, that is monoacetyl purpurea glycoside A. These relationships can be expressed diagrammatically as follows:





Digilanidobiose* fails to give the Keller-Kiliani test, and the presence of glucose in the digilanides, although they contain about the same amount of digitoxose as do the glycosides of the digitoxin type, produces a much fainter response to the digitoxose test.

"Digitoxin is a white or pale buff, odorless, microcrystalline powder. It is insoluble in water and very slightly soluble in ether. One Gm. dissolves in about 40 cc. of chloroform and in about 60 cc. of alcohol."

Digitoxin is rapidly and almost completely absorbed, whereas the other digitalis glycosides are poorly absorbed or may not be absorbed at all. However, digitoxin is especially cumulative more so than the other digitalis glycosides. Given orally, digitoxin is 1,000 times as active as digitalis leaf.²⁴

The average dose is 0.1 mg.

Gitoxin was the second glycoside isolated from *Digitalis purpurea* by Cloetta²⁵ in 1926 and by Krafft²⁶ in 1912.

Digoxin U.S.P. "is a glycoside from the leaves of *Digitalis lanata* Ehrh. or *Digitalis orientalis* (Fam. *Scrophulariaceae*). Digoxin was first isolated from *Digitalis lanata* in 1930 by Smith,²⁷ who at the same time also isolated gitoxin from this same plant. Digoxin per se pre-exists in *Digitalis lanata* as lanatosid-C or digilanide-C²⁴ and differs from the latter in that the sugar moiety has lost a molecule of glucose and acetic acid by hydrolysis.

"Digoxin occurs as colorless to white crystals or as a white, crystalline powder. Digoxin is insoluble in water, in chloroform, and in ether. It is freely soluble in pyridine and soluble in dilute alcohol."

* A disaccharide (composed of digitoxose and glucose) obtained by careful acid hydrolysis.

Digoxin is less cumulative and its duration of action is shorter than that of digitoxin. In an emergency it is claimed that it can be used intravenously in dilute (8 per cent) alcohol.

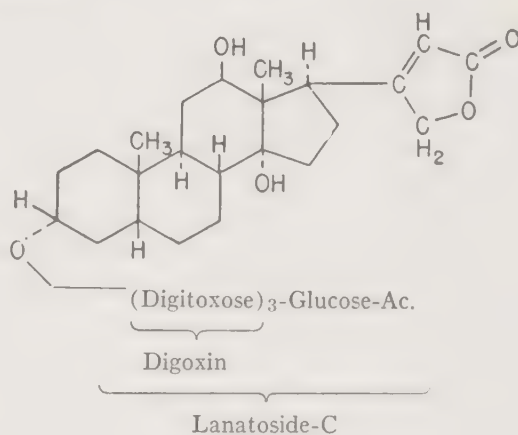
The average dose is 0.5 mg.

Lanatoside-C U.S.P. "is a glycoside²⁴ obtained from the leaves of *Digitalis lanata* Ehrh. (Fam. *Scrophulariaceae*)."

"Lanatoside-C occurs as colorless or white crystals or as a white crystalline powder." It is soluble 1 to 20,000 in water, 1 to 45 in alcohol, 1 to 20 in methanol and 1 to 2,000 in chloroform.

Lanatoside-C is less cumulative and its duration of action is shorter than that of digitoxin. In an emergency it is claimed that it can be used intravenously.

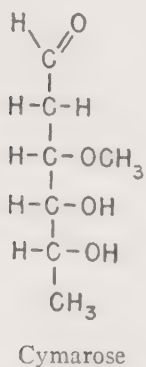
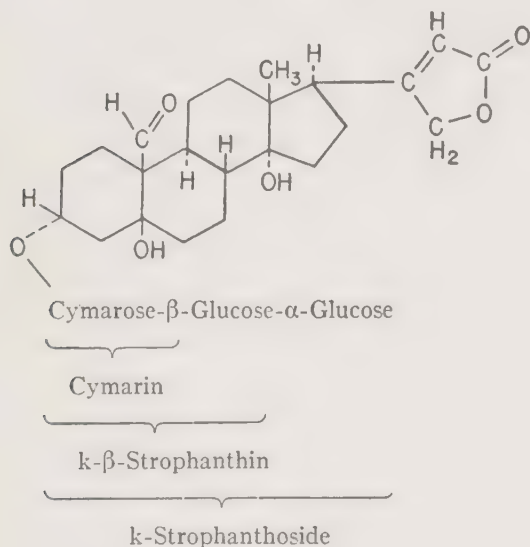
The relationship of digoxin to lanatoside-C can be expressed diagrammatically as follows:



The average dose is 0.5 mg.

Strophanthin N.F. (k-β-Strophanthin). "A glycoside or a mixture of glycosides obtained from *Strophanthus Kombe* Oliver (Fam. *Apocynaceae*). Strophanthin, when assayed as directed, shall possess a potency per mg. equivalent to 0.5 mg. of U.S.P. Ouabain Reference Standard." Of the plants that yield cardio-active substances, the various *Strophanthus* species, particularly, are characterized by the relatively very high glycoside content. Although strophanthin is readily isolated from *Strophanthus Kombe*, 90 per cent of the cardio-active constituents

are present as k-strophanthoside,²⁴ which can be isolated by careful handling during isolation. k-Strophanthoside is very soluble in water and in methyl or ethyl alcohols. Prior to the isolation of this glycoside, k- β -strophanthin was thought to be the chief glycoside from *Strophanthus Kombe*. Cymarine is a glycoside found in Canadian hemp. The following formulae show some relationships between these three compounds.



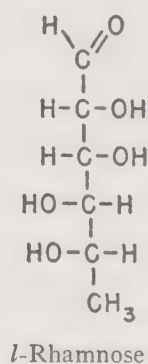
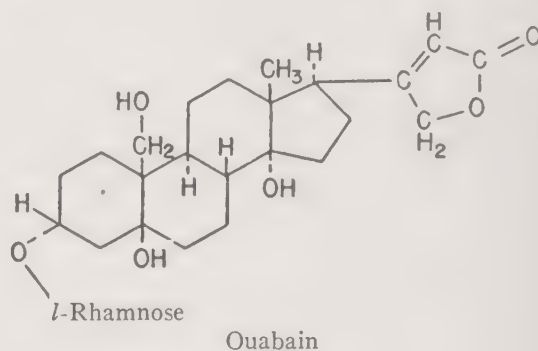
"Strophanthin is a white or yellowish powder containing varying proportions of water. It is stable in air, but is affected by light. Strophanthin dissolves in water and in diluted alcohol, but is less soluble in dehydrated alcohol. It is nearly insoluble in chloroform, in ether, and in benzene."

Strophanthin is used intravenously in emergencies for its cardiac effects.

The average dose (intravenous) is 0.5 mg.

Ouabain (G-Strophanthin) U.S.P. "is a glycoside obtained from the seeds of *Strophanthus gratus* (Wall. et Hook.) Baillon (Fam. Apocynaceae)."

The following formula has been assigned to ouabain.



"Ouabain occurs as white, odorless crystals, or as a crystalline powder. It is stable in air, but is affected by light. One Gm. of Ouabain dissolves slowly in about 75 cc. of water, and in about 100 cc. of alcohol."

Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe. It is used intravenously for its cardiac effects in emergencies.

The average dose (intravenous) is 0.25 mg.

Digalen N.N.R. is the cardio-active principle of digitalis as isolated by Cloetta. It is a highly purified preparation marketed as a colorless or slightly yellowish solution (1 cc. equals 1 cat unit) or in tablet form ($\frac{1}{2}$ and 1 cat unit each).

Digifolin N.N.R. is a digitalis preparation containing the therapeutically desirable constituents of digitalis leaf. It is an amorphous, brownish powder that is soluble in water and in methyl and ethyl alcohols. It is sold in tablets (1 cat unit each) and as a solution in 12 per cent alcohol (1 cc. equals 1 cat unit).

Digilanid N.N.R. is a mixture of the isomorphous crystallized cardio-active glycosides lanatosid-A (47 per cent), lanatosid-B (16 per cent) and lanatosid-C (37 per cent) obtained from the leaves of *Digitalis lanata*. It is a white, odorless powder that is very slightly soluble in water (1 in 10,000). It is sold in tablet form (0.33 mg. equals 1 cat unit) and in solution (1 cc. equals 1 cat unit).

Digipoten N.N.R. is a mixture of the digitalis glycosides in soluble form. It is a pale green powder that is soluble in water and in 25 per cent alcohol. It is sold in 50 mg. tablets ($\frac{1}{2}$ U.S.P. Unit) and in 0.1 Gm. capsules (1 U.S.P. Unit).

Digitalin "German" N.N.R. is a mixture of glycosides obtained from digitalis seeds according to the process of Walz. It consists largely of digitonin, with true digitalin and other glycosides. It is a yellowish-white, amorphous powder that is soluble in water and alcohol. Note that digitonin is given as a synonym for crystallized digitalin by some manufacturers, and it is to be noted particularly that this is quite different from "true digitalin" or the "crystalline digitaline" of the French Pharmacopeia.

The average dose is 1 to 2 mg.

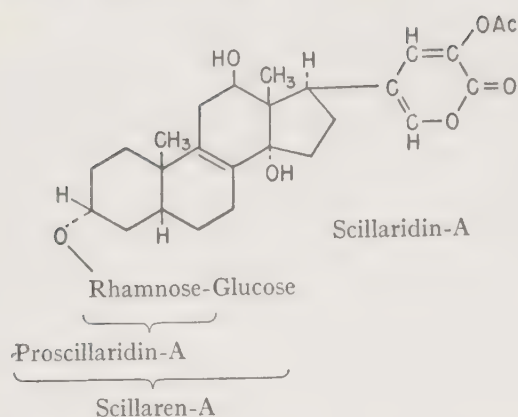
Digitan N.N.R. is a purified extract of digitalis containing the active principles in the same proportions as they exist in the whole leaf. It is digitonin-free, and 85 per cent of the inactive substances present in the ordinary extract have been removed. It is a greenish-yellow, odorless, bitter powder that is insoluble in cold water. The tablets equal 1 cat unit each, and 1 cc. of the tincture equals 1 cat unit.

Gitalin (Amorphous) N.N.R. is a glucosidal constituent of *Digitalis purpurea* prepared according to the method of Kraft. It is a white or slightly buff-colored amorphous powder which is readily soluble in chloroform, ether and alcohol and is slowly soluble in 600 parts of cold water. It is marketed as 0.75 mg. tablets that equal one cat unit.

Scillaren N.N.R. is a mixture of the natural glycosides, scillaren-A and scillaren-B, occurring in fresh squill, *Urginea maritima*, in the proportions in which they exist in the fresh crude drug, i. e., about 2 parts of scillaren-A to 1 part of scillaren-B. It occurs as a white or yellowish-white, odorless, granular powder, possessing a very bitter taste; it is soluble in absolute alcohol (1 in 5) and sparingly soluble in water (1 in 3,000).

Extensive attempts by early workers to isolate the native glycosides of squill resulted only in purified extracts. Thus, the scillipicrin, scillitoxin and scillin of Merk,²⁸ 1879; the scillain of Jarmersted;²⁹ the apparently crystalline substances scillipicrin, scillenin and scillimarin of Waliszewski,³⁰ 1894 and the substances scillitin and scilli diuretin by Kopaczewski,³¹ 1914, were not characterized as pure compounds. Furthermore, the three earlier workers failed to make definite statements concerning their physiologic activity. The successful isolation of the genuine, active, pure cardio-active principles of fresh squill was accomplished by A. Stoll²⁴ and his co-workers in 1933 and 1935 after extensive investigations. His work was assisted by the discovery that the toxicity of the preparations ran parallel to the intensity of the so-called Liebermann's cholesterol reaction. Active and partially purified extracts of squill first show a strong red color, which changes rapidly to blue and then to a bluish-green when the above color reaction is applied.

The following structural formulae are proposed for scillaren-A and its related degradation products.



Acid hydrolysis yields the disaccharide called scillabiose, which is composed of rhamnose and glucose. The enzyme scillaritinase can cleave the glucose residue selectively.

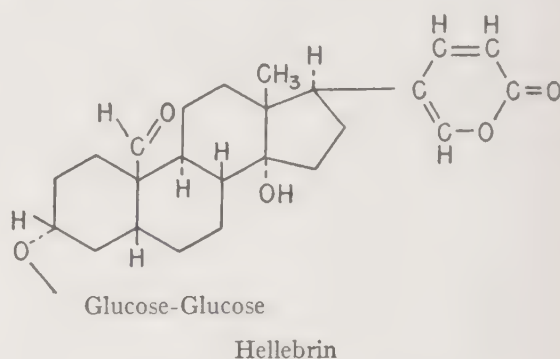
The cardiac action of the scillarens is essentially similar to that of digitalis, but this action is apparently less persistent than that of digitalis. The squill glycosides produce copious diuresis and are often active where digitalis and strophanthin fail to act, or act insufficiently, or where intolerance to digitalis exists. Because of its high therapeutic index and rapid elimination, it maintains compensation in those cases where prolonged treatment is necessary.

Scillaren-B N.N.R. is the amorphous component of the natural mixture of the glycosides occurring in squill, *Urginea maritima*. It is a fine white or slightly yellowish-white, odorless, granular powder, possessing a very bitter taste. It is freely soluble in water and in ethyl and methyl alcohols, 1 in 5 respectively. It is marketed as 0.5 mg. in 1 cc. ampules and used the same as scillaren. Scillaren B is more water-soluble and more active in the frog assay than scillaren A. The ratio of activity is about 3 to 5. Scillaren B is more stable than scillaren A, and the latter accounts for two-thirds of the total quantity of the cardiac glycosides of squill.

Urginin N.N.R. is a mixture of two water insoluble glycosides, urginin-A and urginin-B, derived from squill, in the proportions in which they exist in the drug; i. e., about

equal parts of each. It occurs as a pale yellow, granular powder possessing a slight characteristic odor and an extremely bitter taste. It is soluble in alcohol, and one cat unit is equal to 0.2 mg. per Kg. It is marketed as 1.0 mg. tablets.

Hellebrin, found in *Radix Hellebori nigri*,³² is more active than ouabain when tested in the frog. It is related in structure to the squill glycosides and has been assigned the following tentative formula.



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25

Steroids

STEROLS

PHYTOSTEROLS

BILE SALTS

SEX HORMONES

ADRENAL CORTEX HORMONES

A number of very important compounds that have been found in both plants and animals contain a perhydro-1, 2-cyclopentano-phenanthrene carbon skeleton as part of their molecules. Some of these compounds are sterols, bile acids, sex hormones, corticometric principles, cardiac glycosides, certain saponins and certain toad poisons.

STEROLS

A group of tetracyclic, unsaturated, high molecular weight, secondary alcohols that are closely related in structure occur in all orders of plants and animals, with the possible exception of some bacteria. They are isolated from the unsaponifiable portion of fats. They are insoluble in water but are soluble in the fat solvents. They crystallize in the form of colorless leaflets, platelets or needles, depending upon the solvent from which they are crystallized. They are somewhat waxy in nature. Sterols form loose associations with each other, their own esters and derivatives, the bile acids, the saponins, and with such unrelated substances as urea, substituted ureas, glycerol, maleic and citra-

conic anhydrides and solvents of crystallization. These many associations increase the difficulties in obtaining absolutely pure sterols. Furthermore, upon this property of sterols to enter into these associations may depend, in part, their role in physiologic processes. With many saponins they form crystalline, nonhemolytic, insoluble products.* Therefore, by using digitonin, a digitalis saponin, it is possible to separate out most sterols from unsaponifiable mixtures. The insoluble products readily can be resolved into their component parts in one of several ways.¹ Sterols, even in minute amounts, give characteristic color reactions² with certain reagents. These tests can be used both qualitatively and quantitatively.

Table 42 (page 391) was compiled in order to illustrate by a few examples some of the various sterols found in nature.

An examination of the structural formula for cholesterol as a representative sterol reveals that it has eight asymmetric centers: C₃, C₈, C₉, C₁₀, C₁₃, C₁₄, C₁₇ and C₂₀ with 2⁸ or 256 possible isomers. In cholestanol

* A property of the secondary alcohol group when it is cis to the methyl group at C₁₀. See the formula for cholesterol.

TABLE 42. SOME STEROLS FOUND IN NATURE

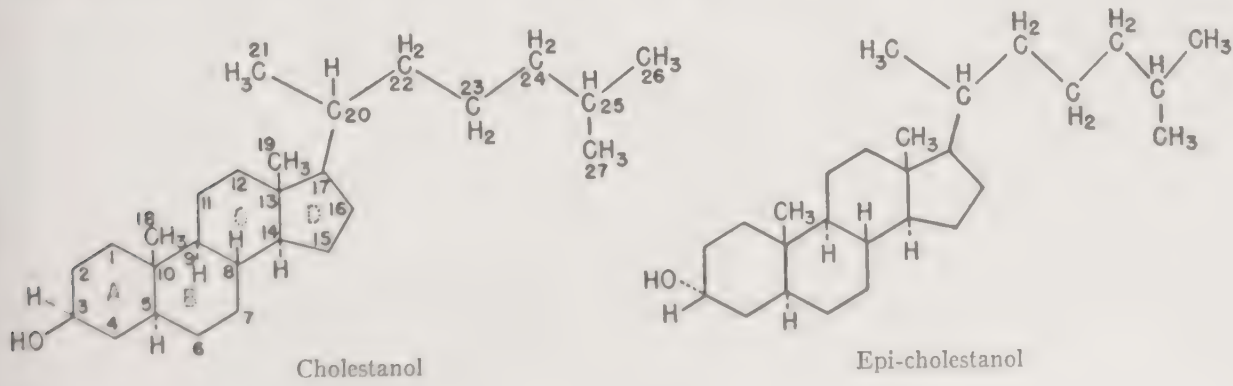
SOME STEROLS FROM THE ANIMAL KINGDOM					
STEROL	SOURCE	M.P. (°C.)	[α] _D	Acetate M.P. (°C.)	Acetate [α] _D
Cholesterol	Animals				
Ostreasterol	Molluscs	142-3	— 45.94	134-5	
Coprosterol	Feces in Man				
Microcionasterol	<i>Microcionia prolitera</i>	126.7	— 19.76	125-6	
Spongosterol	Sponges	124	— 19.59	124	
Clionasterol		137-8	— 37.04	133.4	
Actinasterol	<i>Anemonia sulcata</i>	145-6	— 42.5	126.5	
Stellasterol	<i>Asterias rubens</i>	154-5	+ 3	155-7	
7-Dehydrocholesterol	Animals				

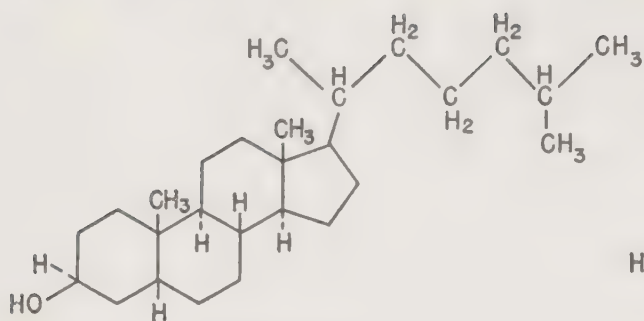
SOME STEROLS FROM THE KRYPTOGAMS					
Ergosterol	Ergot and Fungi	160-2	—123		
Fungisterol	Ergot	144-6	— 20	158	
Zymosterol	Yeast	108-9	+ 47.3	106-7	— 33.5
Cerevisterol	Yeast	265.3	— 57.4	171	— 16.3
Kryptosterol	Yeast	135-6	+ 64		
Fucosterol	Algae	124	— 38.4	118-9	— 43.8

SOME STEROLS FROM THE PHANEROGAMS					
α-Sitosterol	Wheat germ	138-141	— 23.41	122-3	— 29.8
β-Sitosterol	Wheat germ	136-7	— 36	125-6	— 41
γ-Sitosterol	Wheat germ	147-8	— 42.0	143-4	— 4.5
α ₁ -Sitosterol	Wheat germ	166	— 1.7	137	+ 49
α ₂ -Sitosterol	Wheat germ	156	+ 0.55	126	+ 17
α-Tritisterol	Wheat germ	114-5	+ 54.3	107-8	+ 70.4
β-Tritisterol	Wheat germ	97	+ 49.2		
Stigmasterol	<i>Physostigma venenosum</i>	170	— 45.0	141	
α-Spinasterol	<i>Brassica oleraceae</i>	168-9	— 1.8	177-181	— 4.7
β-Spinasterol	<i>Brassica oleraceae</i>	150-4	+ 7.2	145-8	+ 7.65
γ-Spinasterol	<i>Brassica oleraceae</i>	160	0	140	— 14.1
Calosterol	<i>Calotropis gigantea</i>	203-3	+100.6	211-2	+105
Brassica Sterol	<i>Brassica Rapa</i>	148	— 64.4	157.8	
Campesterol	Soyabean oil	157-8	— 33	137.8	— 37

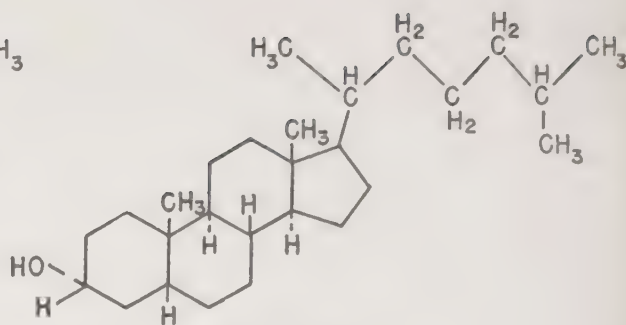
(double bond between C₅ and C₆ in cholesterol reduced) an additional assymmetric center at C₅ is introduced, which increases the number of isomers possible to 512. Step-wise reduction of Δ⁴-cholestenone and Δ⁵-

cholestenone, obtained from cholesterol, yields cholestanol, epicholestanol, coprostanol and epi-coprostanol. These four alcohols differ only in the orientation of the groups attached to C₃ and C₅.





Coprostanol



Epi-coprostanol

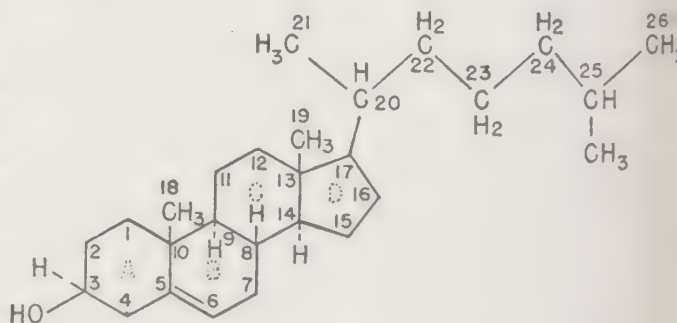
The naturally occurring substances that have a steroidal (cyclopentanophenanthrene) nucleus are closely related in structure in so far as this polycyclic ring system is concerned, i.e., ring D is trans to ring C and ring C in turn is trans to ring B. In the saturated series, both the cis and trans fusions of rings A and B are found. Naturally occurring compounds are known where the C₃-OH is normal (cis to the methyl group at C₁₀) and where it is epi (trans to the methyl group at C₁₀).

Cholesterol U.S.P. (Cholesterin). Cholesterol, the principle sterol of animals, occurs in the tissues of the most diverse phyla. It appears to be present in all metazoa. In some of the sponges it occurs with sitosterol, and in certain molluscs it occurs with ostreasterol. The oyster, *Ostrea virginica*, contains only ostreasterol, which is a doubly unsaturated sitostanol. Gall stones are frequently almost pure cholesterol, and brains and spinal cord, which are rich in cholesterol, furnish the commercial source of supply. The lipid-soluble portion of brains and spinal cord are saponified, and the cholesterol, which is concentrated in the nonsaponifiable portion, is crystallized from organic solvents such as alcohol, ethers, etc. Cholesterol may contain very small amounts of 7-dehydrocholesterol, which is unstable upon prolonged exposure to light and oxygen, therefore, imparting a yellow color to it. This slight color change is not deleterious to the usefulness of cholesterol.

Cholesterol, which is perhaps the most important of all sterols, was first isolated

from gall stones by Paulleitier de la Salle in about 1770. In 1815, Chevreul³ showed that cholesterol was unsaponifiable, and he called it cholesterin (chole, bile; stereos, solid). In 1859, Berthelot⁴ established its alcoholic nature, and since then it has been properly designated in the English nomenclature as cholesterol.

Cholesterol occurs as white or faintly yellow, almost odorless, pearly leaflets or granules. It usually acquires a yellow to pale tan color on prolonged exposure to light or to elevated temperatures. It is insoluble in water and sparingly soluble in alcohol; it is soluble in vegetable oils and most organic solvents.



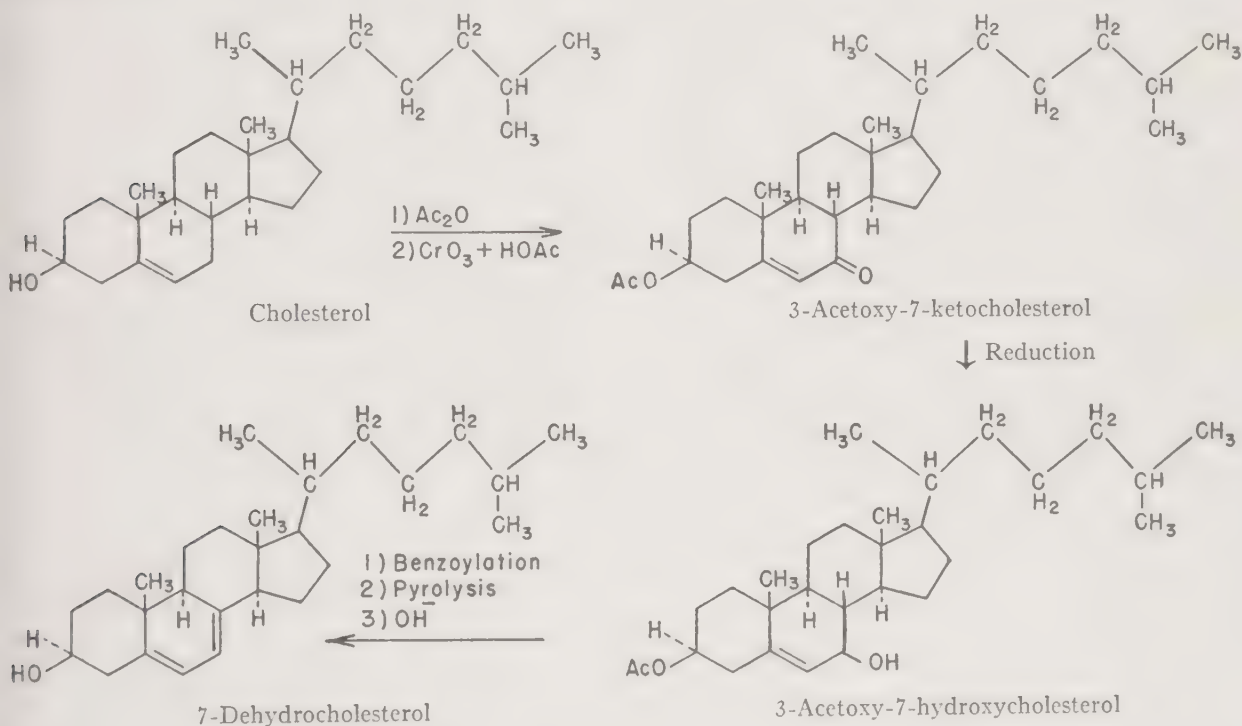
Cholesterol

Cholesterol is stable under normal storage conditions. Because it is an unsaturated secondary alcohol, it might possibly add iodine from ointments containing the same.

Animals are unable to utilize plant sterols, and all cholesterol found in animals is synthesized by them from precursors other than sterols. It is believed that the bile acids, sex hormones, corticometric principles, etc., are synthesized by the body from cholesterol. Part of the cholesterol is excreted in the

feces as coprostanol. Coprostanol differs from cholesterol in that in the former rings A and B are cis and in the latter they are trans.

7-Dehydrocholesterol (Provitamin D₃) occurs in small amounts in the skins of animals. It no doubt also occurs along with cholesterol because the latter, upon irradiation, has antirachitic properties. It occurs in such small amounts in natural sources that they do not furnish a source of supply. However, it can be synthesized from cholesterol as follows:



7-Dehydrocholesterol resembles the sterols in most of its properties except that it undergoes a number of photochemical changes under the influence of ultraviolet light with the generation of a number of products, one of which is vitamin D₃. (See Chap. 28.) 7-Dehydrocholesterol is unstable in clear glass containers under normal storage conditions and it gives rise to degradation products that are very complex in character.

PHYTOSTEROLS

In the years following the isolation of cholesterol from gall stones, cholesterol-like

substances, even though found in plants, were designated as cholesterins or cholesterols. However, Hesse,⁵ in 1878, pointed out that the sterol isolated from peas by Beneke⁶ in 1862 was not identical to cholesterol, and, therefore, he proposed the term phytosterol for those sterols occurring only in plants. Because this term embraced all sterols obtained from the entire plant kingdom and inasmuch as all plant sterols isolated did not exhibit identical physical properties, some investigators chose to name their sterols after the

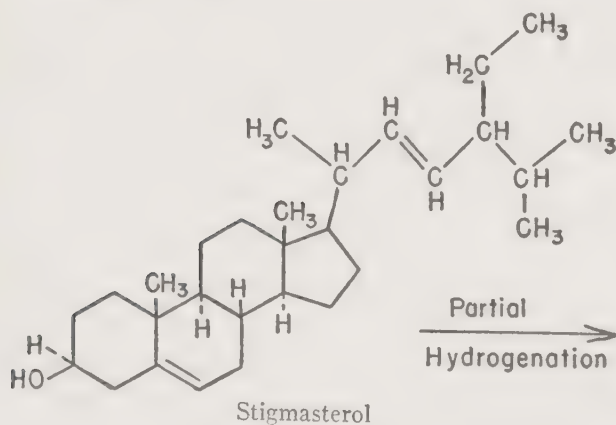
names of the plants from which they were isolated. For example, ergosterol from ergot, stigmasterol from physostigma, sitosterol from wheat, etc. Because the physical properties of many of the phytosterols are very similar to those of the sterol isolated from wheat germ by Burian⁷ in 1897, many phytosterols frequently are designated as sitosterols.

The sitosterols are the most predominantly occurring phytosterols of the Spermatophytes. The name sitosterol has been used, not only to designate the mixture of sterols obtained by Burian in 1897 from wheat

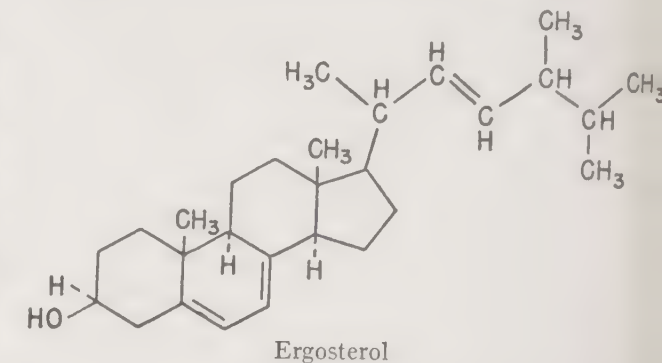
germ, but also those of other phytosterols which, either pure or in a mixture, have physical properties closely resembling those of Burian's phytosterol mixture. The sterol from wheat germ has now been resolved into α -, β -, and γ -sitosterols, dihydrositosterol, α -tritisterol, β -tritisterol, stigmasterol, ergosterol and possibly others. β -Sitosterol occurs as the greater part of the sterols of cottonseed oil and can be prepared somewhat readily in a pure state.⁸

Stigmasterol was first isolated by Windaus and Hauth in 1906 from the sterols found in *Physostigma venenosum*.⁹ They were able to effect a separation because of the insolubility of stigmasterol tetrabromide. It also occurs in quite small amounts in the sterol fractions of many plants. Stigmasterol is important because it contains a double bond in the side chain and, thus, furnishes a somewhat more readily manipulatable starting material for the synthesis of some of the sex hormones and corticometric principles.

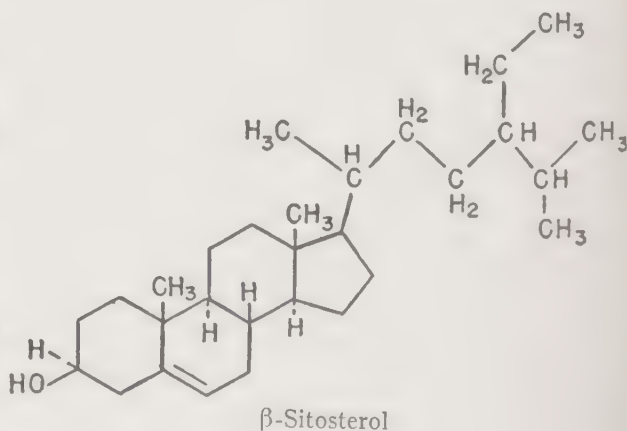
The relationship in structure between stigmasterol and one of the sitosterols can be shown as follows:



Partial
Hydrogenation



Ergosterol undergoes a number of photochemical changes under the influence of ultraviolet light, with the generation of a number of products, one of which is vitamin



In 1889, Tanret¹⁰ succeeded in preparing from ergot, ergosterol that was almost free from the difficultly separable, contaminating fungus sterols. Gerard (1892-1895) demonstrated that ergosterol occurs in many cryptogams such as brown algae, slime fungi, bacteria, mucors, penicillia and lichens. He proposed the rule that ergosterol was characteristic of the cryptogams. Molds and yeasts

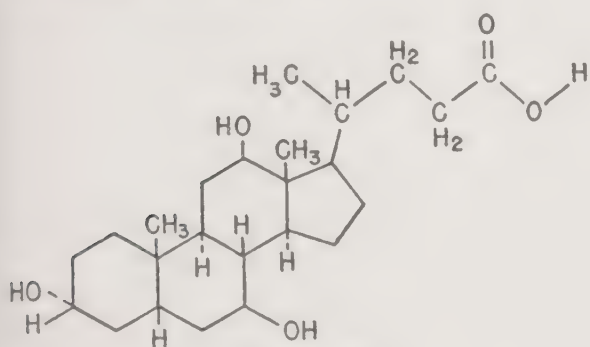
furnish the commercial source of supply of ergosterol. The type of culture media used and the species of fungi grown determine the percentage of ergosterol produced. Thus, for example, *Sacch. Carlsbergensis* yields about 2 per cent ergosterol based upon the dry weight of the organisms. Even though ergosterol is characteristic of the cryptogams, it has been isolated in very small amounts from some phaenerogams.

D₂ (see Chapter 28). Under normal storage conditions, ergosterol in clear glass containers is unstable and gives rise to degradation products that are very complex in character.

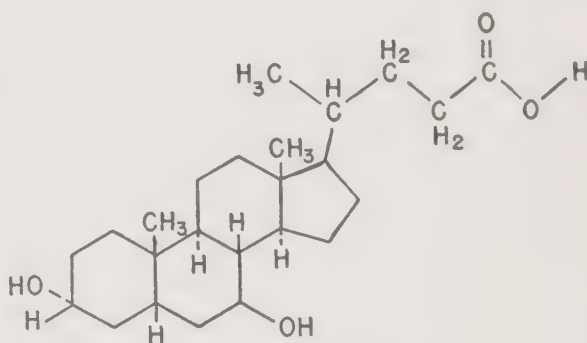
BILE SALTS

The bile of man and a number of animals contains a group of closely related acids, the

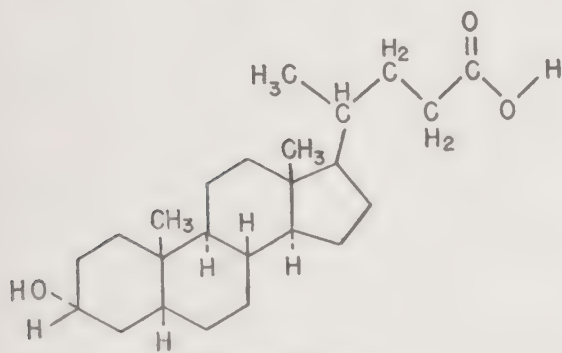
bile acids, conjugated by amide linkages to the common amino acid glycine and the rare amino acid taurine, $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{SO}_3\text{H}$. These conjugates are present as their sodium salts and are called bile salts. These bile salts can be hydrolyzed by alkali to give in the case of ox bile 5 to 6 per cent cholic acid and 0.6 to 0.8 per cent of desoxycholic acid. These acids contain the ring systems found in the sterol coprostanol and are not precipitable by digitonin, even though they have an alcohol group at C_3 . This is due to the fact that C_3OH is trans to the methyl group at C_{10} .



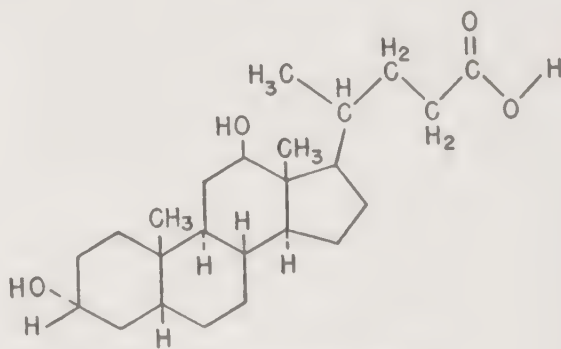
Cholic Acid



Chenodesoxycholic Acid



Lithocholic Acid



Desoxycholic Acid

These acids are stable under normal storage conditions. They are insoluble in water, whereas their sodium salts are both water and alcohol soluble. The secondary alcohol groups can be converted by mild chromic acid oxidation to the corresponding ketones. These keto acids are usually referred to as the dehydro bile acids, i.e., dehydrocholic acid, etc.

Desoxycholic acid possesses to a marked degree the capacity to form stable molecular complexes, the choleic acids. The molar

ratios of the bile acid and the solvent vary with the type of solvent, such as ether, xylene, acetic acid, palmitic acid, stearic acid and even paraffins. Although choleic acids dissociate in dilute solutions in organic solvents until a point of equilibrium is reached, they will dissolve the aqueous alkali without dissociation. If a biologically active material is administered as a solution of the sodium salt of the choleic acid, any effect in the organism appears to be attributable to the liberation and dissociation of the free choleic acid.

Ox Bile Extract (Powdered Oxgall Extract) U.S.P. "Ox Bile Extract contains an amount of the sodium salts of ox bile acids equivalent to not less than 45 per cent of cholic acid."

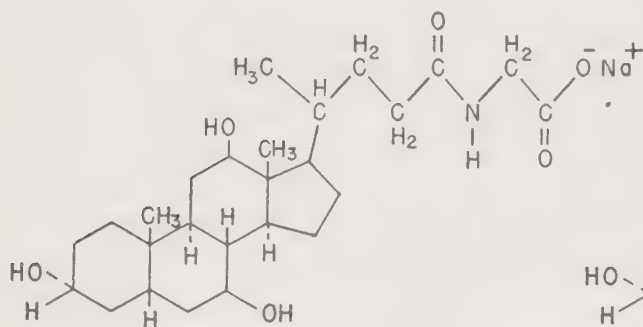
It usually is prepared by extracting dried ox bile with absolute alcohol. Ether is added to the alcoholic extract in order to precipitate the desired bile salts from some of the undesirable ether and alcohol soluble constituents.* This solid extract is composed

* Such as cholesterol, lecithin, bile pigments, etc.

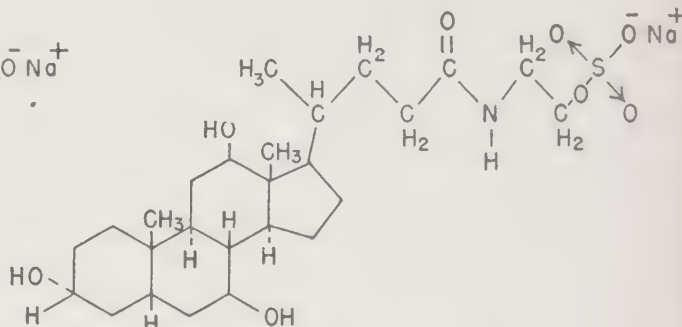
chiefly of the sodium salts of glycocholic and taurocholic acids. They are usually accompanied by varying amounts of bile pigments, i.e., the degradation products of hemin.

Ox Bile Extract is a brownish-yellow,

phylum. This is also true of chologues such as senna. Eighty to 90 per cent of the bile salts in the small intestine are absorbed and recirculated.



Sodium Glycocholate



Sodium Taurocholate

greenish-yellow or brown powder, having a bitter taste. It is soluble in water and in alcohol.

Bile salts are neutral or slightly acidic to litmus and behave as anionic detergents (see surface-active agents). Because sodium glycocholate is the sodium salt of a weak acid, it will be decomposed by mineral acids, etc., and give the water-insoluble glycocholic acid. Bile salts are stable under normal storage conditions, and their aqueous solutions can be sterilized by boiling.

Because the bile salts are surface-active agents, they emulsify water-insoluble fats, fat-soluble vitamins A, D, E and K and other lipoids and thus promote their absorption through the intestinal mucosa. The emulsified fats are more readily hydrolyzed by the lipolytic enzyme lipase and, therefore, more readily assimilable.

It is known that when the flow of bile from the gall bladder into the intestines is obstructed, the absorption of vitamin K is imperfect and a vitamin-K deficiency may result. (See Chapter 28.) Bile salts stimulate the secretory activity of the liver, increasing the flow of both the fluids and solids of bile. They also enhance the efficiency of the resinous hydragogue cathartics such as podo-

The average dose is 0.3 Gm.

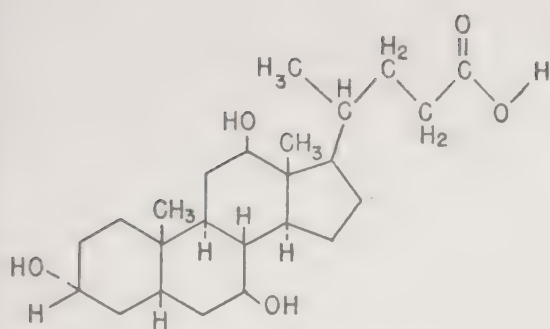
Bile Salts-Fairchild N.N.R. is a preparation obtained from fresh ox bile, consisting of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile.

Glycotauro Bile Salts N.N.R. is concentrated ox bile, freed from bile pigments, containing more than 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate.

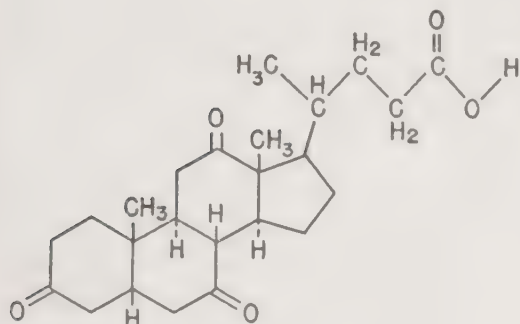
Dehydrocholic Acid N.N.R. (Decholin) is an oxidation product of cholic acid derived from natural bile acids. Because cholic acid is the chief bile acid found upon alkaline hydrolysis of the naturally occurring bile acid conjugates, it can be readily prepared in a pure state by fractional crystallization methods. Cholic acid can be oxidized by means of chromic acid to yield the corresponding 3,7,12-triketocholanic acid, which is commonly called dehydrocholic acid.

Some of the bile acids occur naturally in small quantities as the corresponding dehydroacids. This fact stimulated research in this field with the production and use of dehydrocholic acid.

Dehydrocholic acid occurs as a fine, colorless, crystalline powder with a bitter taste.



Cholic Acid
3,7,12-Trihydroxycholan-2-ic Acid



Dehydrocholic Acid
3,7,12-Triketocholan-2-ic Acid

It is insoluble in water and sparingly soluble in alcohol; it is stable under normal storage conditions and can be sterilized by boiling.

Dehydrocholic acid increases the secretion of a thin, free-flowing bile by the liver, thus facilitating drainage throughout the entire biliary tract. It is not cholagogue in action (stimulate evacuation of the gall bladder). It is, therefore, used to alleviate biliary stasis, functional insufficiency of the liver, outline the bile ducts at operation and in cholecystography to accelerate the appearance of the gall bladder shadow and to hasten removal of residual tetraiodophenolphthalein from the biliary tract. Dehydrocholic acid produces diuresis in edema of cardiac origin but is less effective than the mercurials. It potentiates the diuretic effect of mercurials. It may be used with antispasmodics, if so desired.

The average dose is 0.25 to 0.5 Gm.

Sodium Dehydrocholate (Decholin Sodium) N.N.R., the sodium salt of dehydrocholic acid, is a fine, colorless, crystalline powder with a very bitter taste. It is soluble in water or alcohol, and its aqueous solution is alkaline to litmus. Its actions and uses are the same as those of dehydrocholic acid; however, because it is soluble in water, it can be administered intravenously when necessary.

Ketochol is the keto form of the normal, naturally occurring mixture of bile acids. Its use and actions are essentially the same as those of dehydrocholic acid.

SEX HORMONES

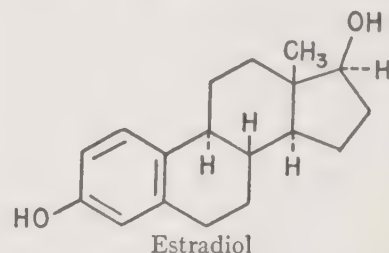
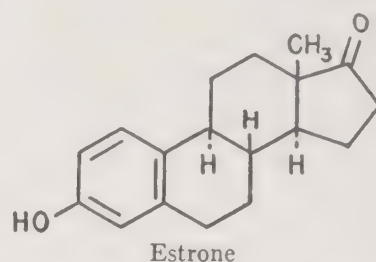
The anterior lobe of the pituitary gland secretes protenoid gonadotropic substances that stimulate the development of the gonads of both the male and female of the species. The gonads, in turn, under this stimulation, continuously synthesize the sex hormones, which have the ring systems found in the sterols and bile acids. In the case of the human female, two gonadotropic hormones are involved, i.e., follicle-stimulating and luteinizing hormones. At maturity, the follicle-stimulating hormone stimulates to maturation the development of the graafian follicle, in which the egg cells or ova develop. Under this developmental stimulation, the cells around the follicle produce the follicular hormone (an estrogenic compound), which is absorbed and circulated by the blood stream throughout the body. After ovulation, the luteinizing hormone stimulates the development of the corpus luteum, which replaces the graafian follicle. Under this developmental stimulation, the corpus luteum produces progesterone, which is absorbed and circulated through the body by the blood stream. If the ovum has been fertilized, pregnancy ensues, and the corpus luteum grows for several months and attains a large size. If, however, pregnancy does not occur, the corpus luteum degenerates, menstrual hemorrhage occurs and the cycle is repeated.

Although α -estradiol is the original estrogenic substance produced by the ovaries, estrogenic substances have been found in other sources; e.g., in the placenta, the adrenals, the testes of the stallion, pregnancy urine of women and mares, stallion urine, urine of men, palm-kernel oil, female willow flowers, suitable extracts of peat, brown coal, lignite, coal tar and petroleum, bile, feces and yeast. The pregnancy urine of women contains 10,000 mouse units per liter, whereas mare's pregnancy urine contains ten times this amount. Stallion urine contains 170,000 M. U. per liter. This is not as paradoxical as it may appear at first, for the steroids excreted in the urine are products of metabolism and not functioning hormones, and it is only in the case of equines that males show a higher excretion of female sex hormones than females. The estrogenic substances found in the female pregnancy urine are oxidation products of α -estradiol.

Estradiol (Dihydrotheelin, Oestradiol) U.S.P. (α -Estradiol, The Follicular Hormone, The Female Sex Hormone). α -Estradiol is believed to be the follicular hormone first synthesized by the graafian follicle of the ovary. Because it is produced continuously in such small quantities by the ovary and is promptly utilized and excreted in a changed form, the ovaries of cattle and hogs cannot be used as commercial sources of supply. It can be prepared by the reduction of estrone, which is one of the excretory products of α -estradiol. It has been synthesized from Δ^4 -androstene-3,17-diol.¹¹

In 1922, Frank¹² discovered in the fluid of the graafian follicle an active estrogenic substance, that is, a substance which, when injected into rodents whose ovaries had previously been removed, produced estrus or sexual heat. Allen¹³ confirmed this work in 1922. Ascheim and Zondek,¹⁴ in 1927, showed that the urine of pregnant women was active in the above test and presented a potential source of supply. Doisy *et al.*¹⁵ in 1929 isolated, from the urine of pregnant

women, a very active crystalline substance that was later known as estrone.



α -Estradiol was actually extracted from sows, ovaries¹⁶ in which it occurs to the extent of 6 mg. per ton or about 1 part in 150,000,000. It has also been isolated from urine of pregnant mares¹⁷ and women¹⁸ and from the human placenta.¹⁹

Estradiol occurs as odorless, white or slightly yellow, small crystals or crystalline powder. It is almost insoluble in water, soluble in alcohol, and sparingly soluble in vegetable oils.

Estradiol and its related products found in urine differ in part from all other naturally occurring steroidal compounds in that ring A is aromatic, and, therefore, the OH group at C₃ is phenolic and exhibits all the properties of phenols; i.e., it will form sodium salts with alkali hydroxides, etc. In the dry state it is quite stable under normal storage conditions and can be sterilized. Because it is phenolic, its stability will be comparable to phenol when in contact with moisture, peroxides of fats and other oxidizing agents.

Allen and Doisy,²⁰ in 1923, developed a convenient method of bio-assay in which the determination is made of the minimum amount of hormone required to give full estrous cycle in castrated female mice or rats. This response is detected by microscopic examination of a stained smear of the vaginal epithelium. This cycle takes place in

four stages, i.e., diestrus (epithelial nucleated cells), proestrus (large nucleated cells accompanied by epithelial cell and cornified cells), estrus (only cornified cells) and post-estrus (vaginal epithelium invaded by leukocytes which make up practically the entire smear). This assay gave rise to mice and rat units as a measure of potency of a preparation. However, because a number of variables, i.e., solvent, number of doses, route of administration, etc., did not give completely uniform results, a crystalline estrone standard was adopted as an International Unit. This I. U. is equal to 0.1 microgram of crystalline estrone and is about equal to one mouse unit. A rat unit is 4 or 5 or even 10 times greater than the mouse unit. α -Estradiol has 120,000 I. U. per mg., whereas β -estradiol is quite inert.

Estradiol is synthesized by ovarian follicles from childhood to the menopause. The peak of secretion of estradiol is at the time of ovulation, and this is no doubt due to the liberation of a large amount of follicular fluid. In the immature female, estradiol accelerates the growth of secondary sex organs, i.e., the vagina, the fallopian tubes and the uterus; the development of the breasts (mammary glands); the development of the genital tract and the distribution of hair. At sexual maturity it plays a role in the development of the uterine wall for reception of the fertilized ovum and arouses sex instinct, i.e., estrus, heat and rut. Therefore, a deficiency of estradiol in the immature female delays the above developments. In the mature female, it maintains the normal size and functional capacity of the uterus, the fallopian tubes and the vagina. Estradiol preserves the normal epithelium of the vulva and the vagina and the muscular activity of the myometrium and the fallopian tubes. It promotes the growth of the duct tissues of the breast, especially during pregnancy. It acts upon the pituitary so as to control the secretion of the gonadotropic and other hormones. Estradiol exerts a powerful influence upon the psychic attitudes and general

health of the adult woman. It plays a role in the maintenance of a normal condition of nasal and oral mucous membranes. It also sustains the basal metabolic rate and has certain vasodilator actions. Estradiol plays a role in the nutrition of unborn and prematurely born children. It also exhibits some corticometric activity, particularly that concerned with fluids and salts.

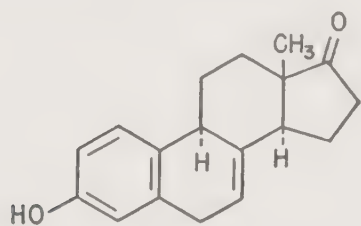
It follows that estradiol therapy is indicated in cases where a deficiency of this hormone is known. Such therapy will bring about a normal state of being. For example, estradiol can be used in the treatment of sexual infantilism, senile vaginitis in elderly women, smoother transition during the menopause, to inhibit the pituitary in certain overactive states and to correct juvenile vaginitis due to a gonococcus. In the latter condition, estradiol effects a brief conversion of the juvenile epithelium to the adult type, which has secretions of a lower pH, is a more rugged kind of tissue and is markedly more resistant to the infection. Estradiol increases muscular strength, bodily vigor and mental acumen.

The symptoms of the menopause with their percentages of incidence are tabulated as follows:²¹

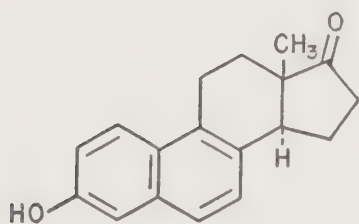
Nervousness, subjective	98.0
Menstrual disturbances	95.5
Flushes and chills.....	95.2
Excitability	88.4
Fatigability and lassitude.....	88.0
Depression and crying.....	81.6
Irritability	79.2
Sleep disturbed	72.3
Tachycardia, palpitation and dyspnea.....	71.3
Vertigo, scotomata	63.3
Decreased memory and concentration.....	62.2
Headaches	47.8
Frigidity	44.7
Numbness and tingling.....	40.3
Occipitocervical aching	40.3
Vague and indefinite pains.....	38.5
Excessive sweating	32.0
Formication	30.7

α -Estradiol is oxidized in the body and excreted in the urine as estrone, estriol, equilin²² and equilenin sulfates and glucuronates and as the free compounds. All these excretory products have estrogenic

activity that is qualitatively equal to that of α -estradiol, but differ quantitatively. Estrone, estriol and equilenin have one-twelfth,²³ one-sixty-sixth²⁴ and one-three-hundred-sixtieth the activities of α -estradiol, respectively.



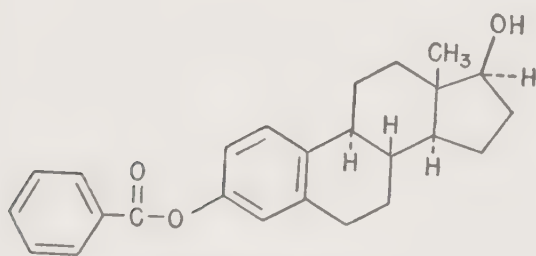
Equilin



Equilenin

The average dose is 0.2 mg.

Estradiol Benzoate (Estradiolis Benzoas, Oestradiol Benzoate) U.S.P. (Progynon-B). Estradiol benzoate is the benzoate of α -estradiol. It is prepared by the benzylation of α -estradiol at the C_3OH .

 α -Estradiol Benzoate

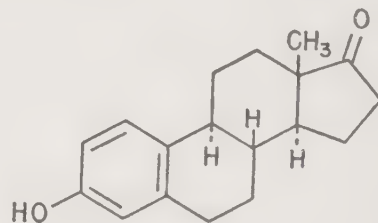
"Estradiol benzoate occurs as a white or slightly yellow to brownish, crystalline powder that is odorless and stable in air. It is almost insoluble in water, soluble in alcohol, slightly soluble in ether and sparingly soluble in vegetable oils."

Of the more common and simple esters, such as the acetate, propionate and benzoate, which prolong the activity of estra-

diol when administered intramuscularly, the benzoate is the most desirable because it is more slowly absorbed. Orally, these compounds have a marked decrease in activity due to destruction by intestinal bacteria and liver.

The average dose (intramuscular) is 1 mg.

Estrone (Estronum, Theelin) U.S.P. (Estrogenic Hormone, Estrin, Folliculin, Progynon, Menformon and Thelykinin). Estrone is obtained from pregnant women's and mare's urine and from stallion urine. Because much of the estrone is conjugated as the sulfate,²⁵ the urine must first be hydrolyzed before extraction with organic solvents. The estrone is purified²⁶ by the use of Girard's reagent,²⁷ adsorption techniques and fractional crystallization processes. It also is synthesized from cholesterol but by a none too practical procedure.



Estrone

3-Hydroxy-17-keto-estrane

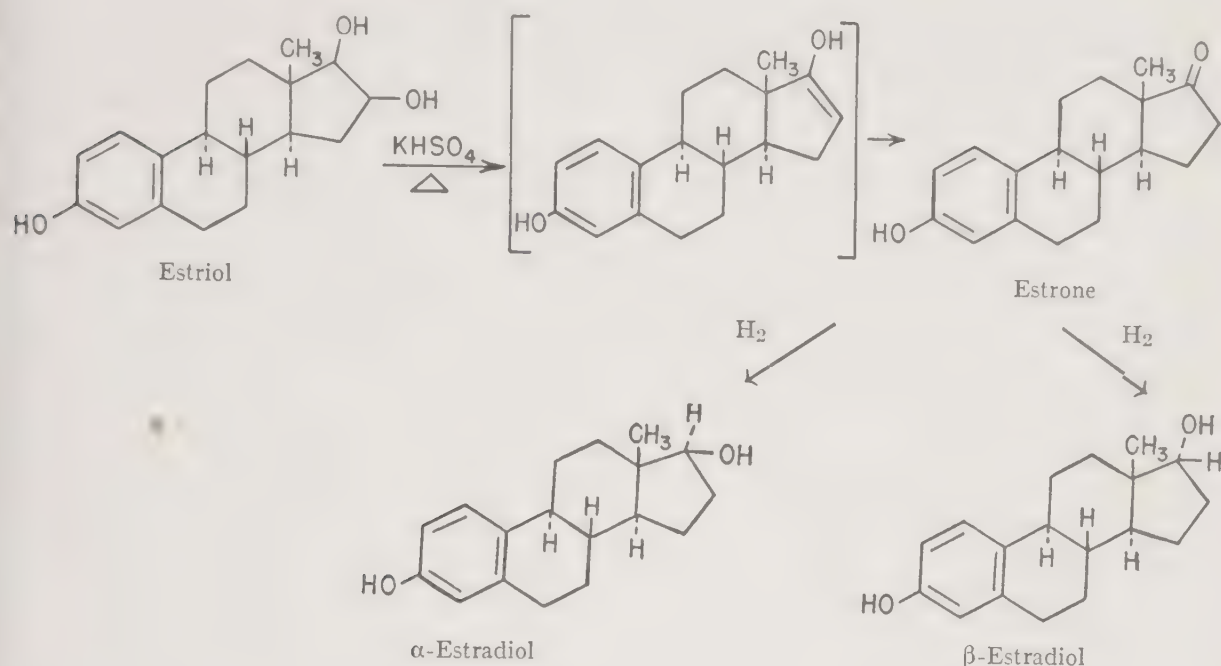
Estrone occurs as small, white crystals or as a white crystalline powder that is odorless and is stable in air. It is slightly soluble in water but is soluble in alcohol and in solutions of fixed alkali hydroxides.

The maximum activity of estrone can be obtained when it is administered intramuscularly. Orally, its activity is greatly reduced because intestinal bacteria and the liver oxidize it to produce substances with lowered activities.

The average dose (intramuscular) is 1 mg.

Estriol (Theelol) N.N.R. Estriol is 3, 16, 17-trihydroxy estrane. It is obtained from the same natural sources as estrone. It was first isolated by Doisy²⁸ and others in 1930 and was secured as the glucuronate

in 1935.²⁹ Estriol can be converted to estrone and the estradiols by the following reactions.



Estriol occurs as a white, odorless, microcrystalline powder. It is practically insoluble in water, soluble in alcohol and vegetable oils.

Estriol is used orally for its estrogenic activity, which is one-sixty-sixth that of α-estradiol.

The average dose is 0.06 to 0.12 mg.

Estrogenic Substances (Premarin) N. R. is an amorphous preparation containing the naturally occurring, water-soluble, conjugated forms of the mixed estrogens obtained from the urine of pregnant mares. This preparation contains chiefly estrone sulfate together with small amounts of other equine estrogens and relatively large quantities of nonestrogenic material.

Premarin is prepared by extracting concentrated, pregnant mare's urine with butyl alcohol and subsequently removing the non-desirable alkali-soluble constituents from the butyl alcohol with tenth normal sodium hydroxide. After the butyl alcohol is removed, the solid residue is treated with acetone. The acetone solution is concentrated and then mixed with an excess of

ether to precipitate the desirable constituents as an amorphous reddish-brown to

almost white powder. This powder is soluble in water and alcohol but is insoluble in oils and ether.

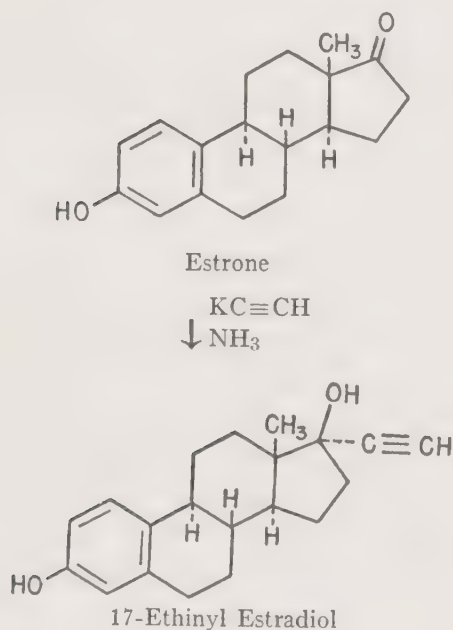
Premarin is used orally for its estrogenic activity. Apparently the sulfates of the estrogenic substances are not as readily oxidized by intestinal bacteria and the liver as are the free estrogens because they may be more readily absorbed and circulated in the blood stream.

Estrogenic Substances (Amniotin) N. R. is a highly concentrated, noncrystalline preparation of estrone together with a small varying amount of other estrogenic phenolic ketones extracted from the urine of pregnant mares. Pregnant mare's urine is hydrolyzed by boiling with hydrochloric acid at a pH of 1.5 for three hours and subsequently extracted with ethylene dichloride. The solid extract obtained by the removal of the ethylene dichloride is dissolved in ether and washed with weak alkali. The ether is removed, and the residue is dissolved in toluene, from which the active constituents are extracted by means

of normal sodium hydroxide. The alkaline solution is acidulated, and the precipitate obtained is extracted with toluene. The toluene is removed, and the residue is further purified by high vacuum distillation. The purified materials are dissolved in sterile vegetable oil for hypodermic and oral use and are incorporated in a glycerogelatin base for vaginal administration.

Amniotin is used for its estrogenic activity.

Ethinyl Estradiol (Estinyl) N.N.R. is made by treating estrone with potassium tertiary amylate in acetylene or potassium acetylide in liquid ammonia as follows:³⁰



Because estradiol and estrone have weak oral activity due to the attack of positions 16 and 17 by bacteria in the intestines and liver, the introduction of an acetylene group at position 17 protects the molecule from this attack without materially reducing its estrogenic activity. It therefore becomes an effective, orally active estrogenic compound whose basic structure is that of the naturally occurring α -estradiol. Ethinyl estradiol is equal to estradiol in potency when it is administered subcutaneously; however, it is 15 to 20 times as active when given orally.

Ethinyl estradiol exhibits side reactions such as nausea, vomiting, dizziness and nerv-

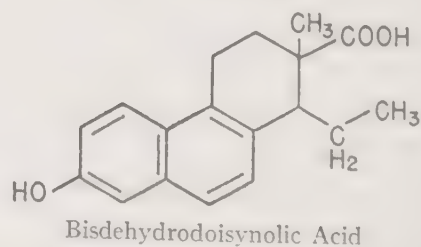
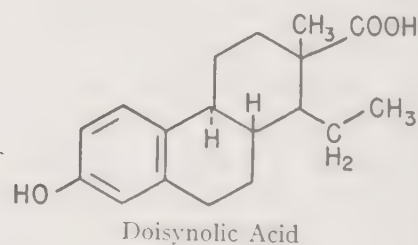
ousness. These side reactions can be avoided in 93 per cent of the patients by the use of smaller doses.

A dosage of 0.05 to 0.15 mg. daily is adequate for the average patient.

The following table gives the quantity in mg. of estrogens given per week that are necessary to induce withdrawal bleeding, when given for three weeks, in approximately 50 per cent of the trials.³¹

Ethinyl estradiol orally.....	0.40
Estradiol dipropionate intramuscularly..	0.86
Estradiol monobenzoate intramuscularly.	1.06
Estradiol monopropionate intramuscularly	1.75
Estradiol orally	13.40
Estrone intramuscularly	3.00
Estrone orally	31.50
Sodium estrone sulfate orally.....	17.50
Sodium estriol glucuronide orally (oral units)	42,000
Mixed estrogens orally (I. U.).....	126,000
Stilbestrol orally	3.00
Monomethoxy stilbestrol orally.....	35.00
Hexestrol	10.50

Doisynolic acid (1-ethyl-2-methyl-7-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthryl-2-carboxylic acid) and **bisdehydrodoisynolic acid** (1-ethyl-2-methyl-7-hydroxy-1,2,3,4-tetrahydrophenanthryl-2-carboxylic acid) have been obtained by the fusion with potassium hydroxide of estrone and equilenin respectively.³²

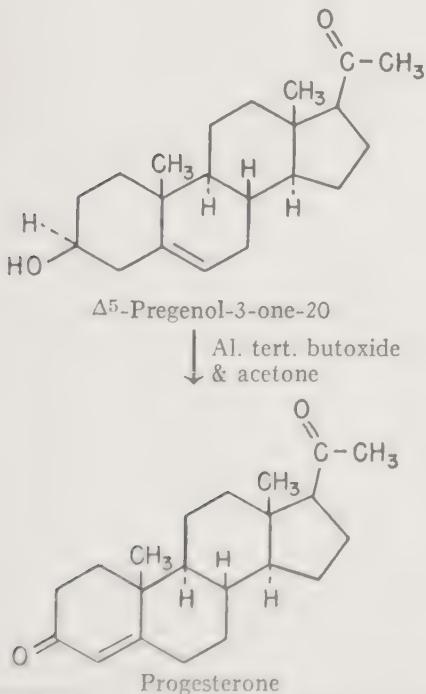


Both of the above-mentioned compounds have been synthesized.³² These compounds, particularly doisynolic acid, exhibit high

estrogenic activity. Doisylic acid, when bio-assayed by the Kahnt-Doisy method, using pure estrone as a standard, gave the typical estrus response in doses of 0.8 to 0.9 micrograms. It is very effective when administered orally.³³

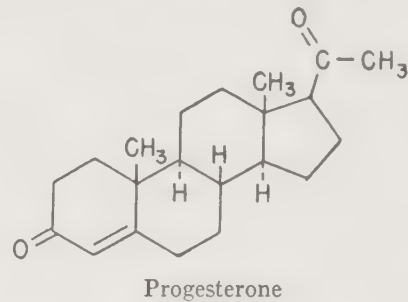
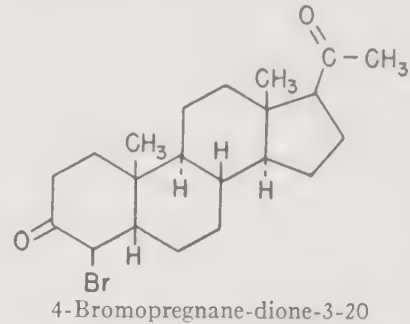
Progesterone U.S.P. (Progestin, Corpus Luteum Hormone, Oestrogenic Hormone) is Δ^4 -pregnen-3:20-dione. Progesterone is thought to be the original hormone produced by the corpus luteum. It also has been found in the adrenal glands and in the placenta. To date it has not been found in isolatable quantities from any other source. Like the other hormones, it is continuously elaborated and promptly utilized, and the above sources contain such small amounts* that they cannot furnish a practical source of supply.

Progesterone is prepared on a commercial scale from cholesterol, stigmasterol³⁴ and the sapogenins. Δ^5 -Pregnenol-3-one-20 is obtained as a by-product of the technical oxidation of cholesteryl acetate dibromide in the production of dehydroisoandrosterone, which is used in the synthesis of testosterone. Δ^5 -Pregnenol-3-one-20 is converted to progesterone by an Oppenauer oxidation as follows:



* 1:40,000 in the human corpus luteum and 1:75,000 in the placenta.

In the synthesis of testosterone from the sapogenins,³⁵ one of the intermediates, 4-bromopregnane-dione-3-20, is heated with pyridine to give progesterone. (See the synthesis of testosterone.)



Fraenkel,³⁶ as early as 1903, showed that the corpus luteum was essential for the maintenance of pregnancy. Corner and Allen,³⁷ in 1930, prepared active extracts of corpora lutea capable of functionally replacing the organ. Butenandt,³⁸ in 1934, isolated progesterone from the corpus luteum, and Beall³⁹ isolated it from the adrenal glands in 1938.

Progesterone occurs as a white crystalline powder that is colorless and stable in air. It is practically insoluble in water, but is soluble in alcohol and acetone and is sparingly soluble in vegetable oils.

Progesterone is sensitive to alkalis or to light and should be stored in tight, light-resistant containers. It can be sterilized by means of heat.

Progesterone plays a role in the pronounced growth or thickening of the mucous membrane on the inner wall of the uterus.⁴⁰ This thickening prepares for the reception of the fertilized ovum in the event of fertilization or pregnancy. In the event of pregnancy, progesterone is secreted throughout

gestation, the first 3 months by the corpus luteum and the remainder of the time by the placenta. After fertilization, progesterone suppresses ovulation, inhibits uterine motility in threatening abortion and functional dysmenorrhea, induces favorable conditions for growth and development of the fetus, plays a role in the development of the mammary gland and prevents estrus cycle in lower animals and menstruation in women. Progesterone has some corticometric activity and is thought to antagonize, to a certain extent, estrogenic activity.

Progesterone should prove useful in those conditions in which there is deficiency of it in the body or when a more pronounced progesterone activity is desired.

Progesterone is administered intramuscularly in order to obtain the maximum effect. Orally its activity is of a low order.

The average dose (intramuscular) is 5 mg.

Progesterone is excreted chiefly as the reduction product pregnandiol [pregnandiol-3 (α), 20 (α)]. It has been found in the pregnancy urine of man, cows, mares and monkeys.

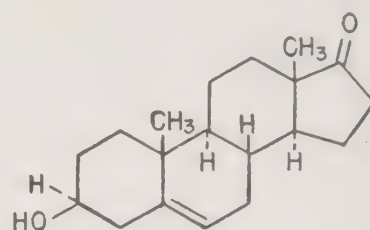
The following inactive compounds, which probably originate from progesterone, also have been isolated.⁴¹

COMPOUND	SOURCE
Pregnandiol glucuronide	Nonpregnancy urine of man and bulls
Allopregnandiol-3 (α), 20 (α)	Pregnancy urine of man, cows and mares
(Allo-pregnandiol)	
Pregnanol-3 (α)	Pregnancy urine—man, cows and mares
Allopregnanol-3 (β), 20 (α)	Nonpregnancy urine—bulls
Pregnanol-3 (β)-one-20	Pregnancy urine—man, cows
Allopregnanol-3 (α)-one-20	Pregnancy urine—man
Allopregnanol-3 (β)-one-20	Corpus luteum, adrenals. Pregnancy urine—man, mares and cows
Pregnandion-3,20	Pregnancy urine—mares
Allopregnandion-3,20	Pregnancy urine—mare

Desoxycorticosterone when fed to a chimpanzee was recovered largely as pregnandiol-3(α), 20(α) from the hydrolyzed urine. If this is true, it is possible that some of the above excretory products may have their origin from the corticometric principles.

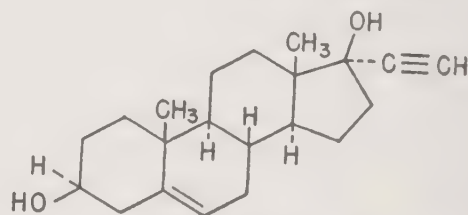
Progesterone exhibits a high degree of specificity, and slight changes in the structure of the molecule lead to inactive products.

Anhydrohydroxyprogesterone (Ethisterone) U.S.P. (Pranone). Anhydrohydroxy-

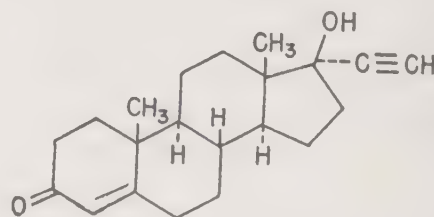


Dehydroisoandrosterone

↓ $\text{KC}\equiv\text{CH}$ in
liquid ammonia

17-Ethynyl Δ^5 -androstendiol-3(β)-17(α)

↓ Al. tert. butoxide
and acetone



Anhydrohydroxyprogesterone

progesterone is Δ^4 -pregnene-17-one-17(α)-ol-3-one or 17-ethynyltestosterone and is prepared as shown above.

Anhydrohydroxyprogesterone occurs as white or slightly yellow crystals or as a crystalline powder that is odorless, stable in air but is affected by light, particularly in the presence of alkali. It is practically insoluble in water, slightly soluble in alcohol and ether and in vegetable oils.

Anhydrohydroxyprogesterone possesses the same activity as progesterone; however, it is orally active. This is due to the fact that the ethinyl group at C_{17} is not attacked by intestinal bacteria, liver, etc., as is the acyl side chain at C_{17} in progesterone, thus resulting in the production of inactive compounds.

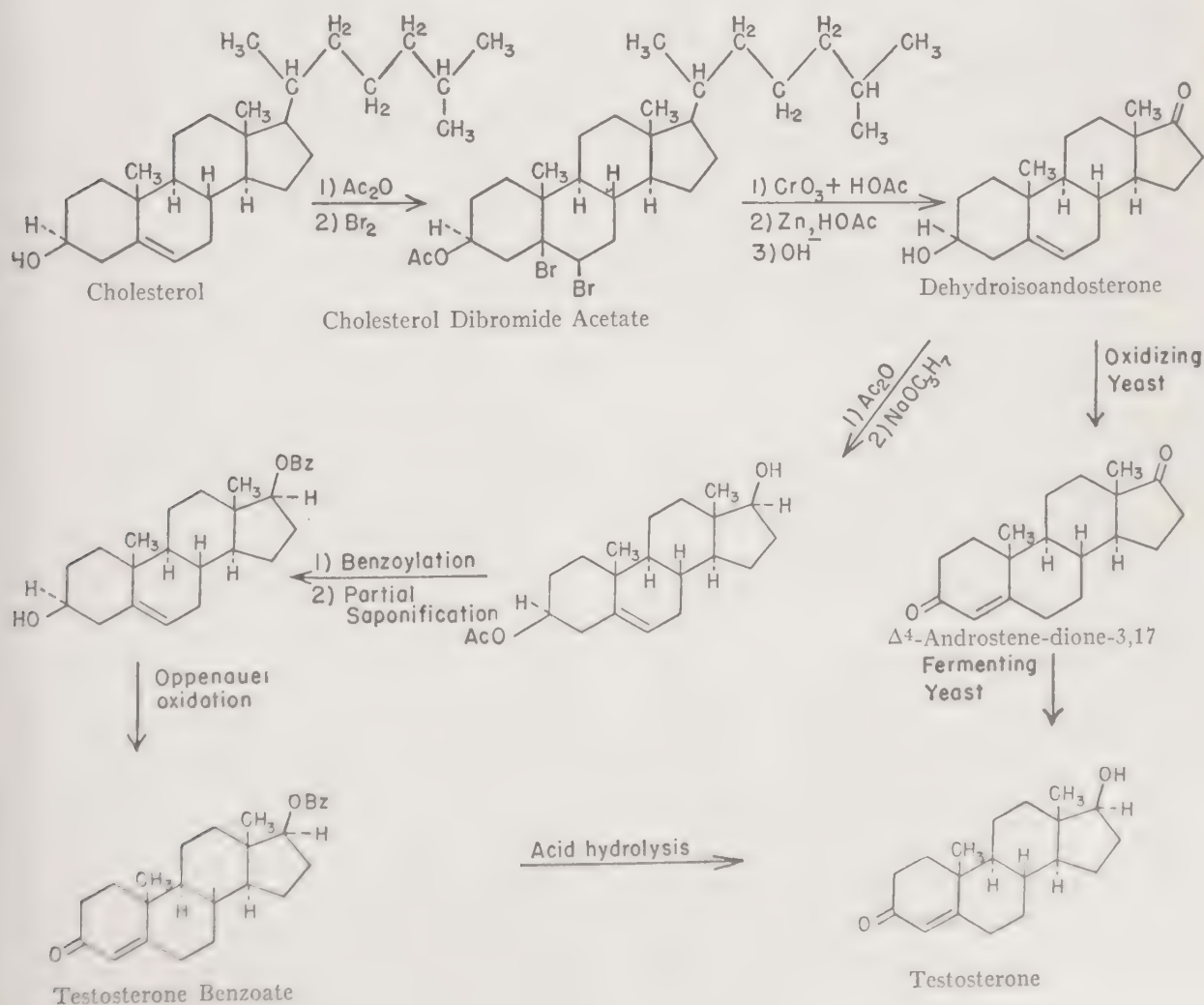
The average dose is 10 mg.

In the case of the male, there is one gonadotropic hormone which functions in stimulating the development of the testes. Under this stimulation, the interstitial cells, lying outside of the seminiferous tubules and not concerned with spermatogenesis, continuously produce very small quantities of the male sex hormone, testosterone, which is absorbed and circulated by the blood stream throughout the body. The term androgenic hormones is applied to those substances

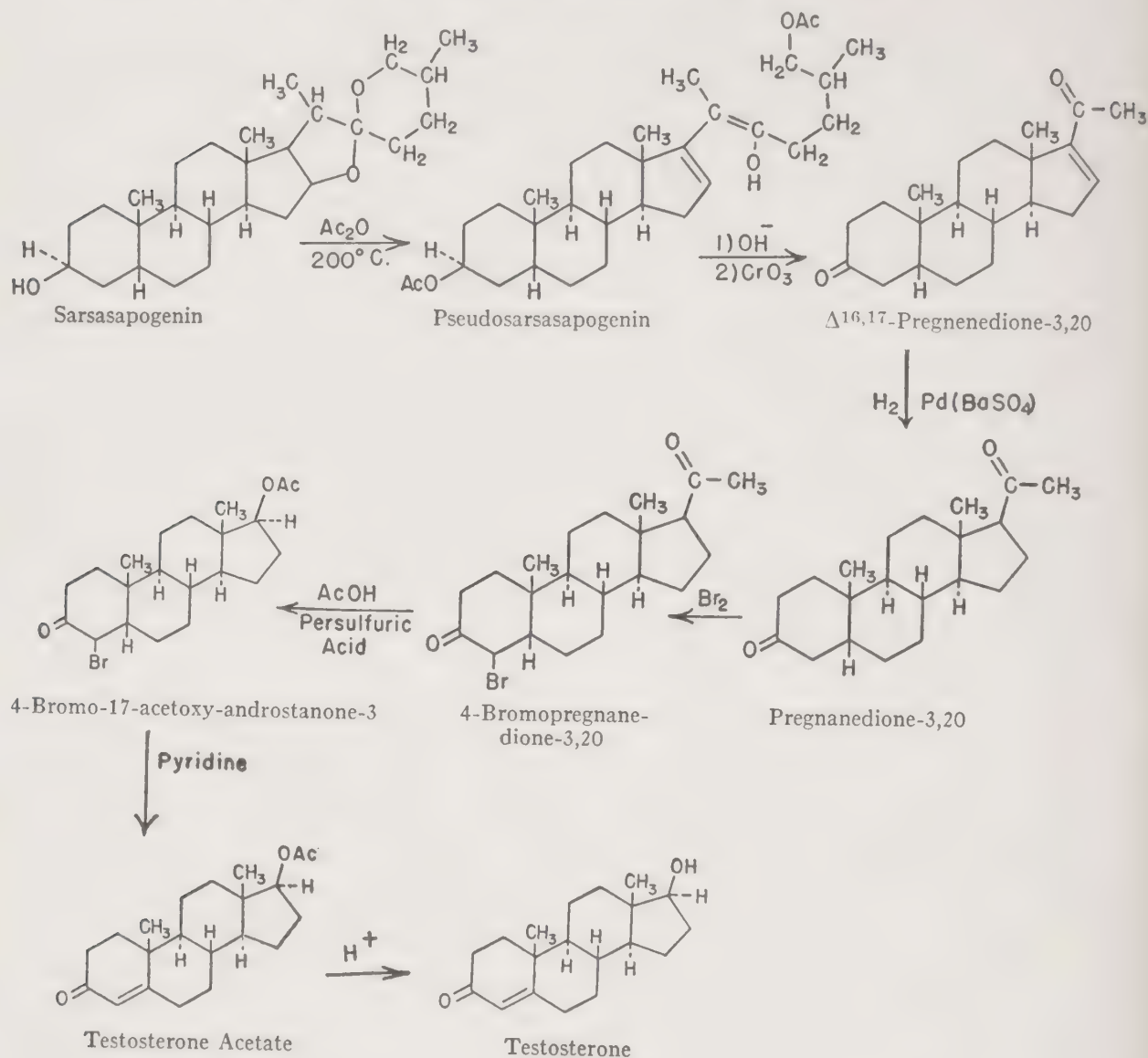
whose activities are comparable to those of testosterone.

Androgenic substances also occur in the urine of human males and females and also are found in the urine of horses, both male and female.

Testosterone occurs in such small amounts in testes that Laqueur,⁴² in 1935, first isolated it by working with large quantities of bull testes. About 90 to 270 mg. are present in a ton of testes.⁴³ Therefore, this is not a practical source of supply. In fact, there is no natural source rich enough in testosterone to be of preparative value. However, testosterone is synthesized in commercial quantities from the androgenic excretory products found in stallion urine, cholesterol and some of the saponogenins, i.e., sarsasapogenin and diosgenin. Its synthesis from cholesterol can be depicted as follows.^{44,45}



Testosterone can also be prepared from sarsasapogenin as follows:⁴⁶



Testosterone is a white, odorless and tasteless, crystalline powder. It is insoluble in water but soluble in alcohol, vegetable oils and organic solvents. It is stable in air under normal storage conditions. It is sensitive to alkali.

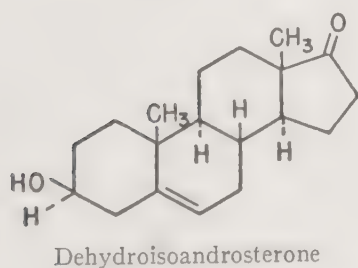
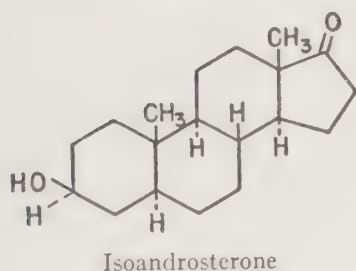
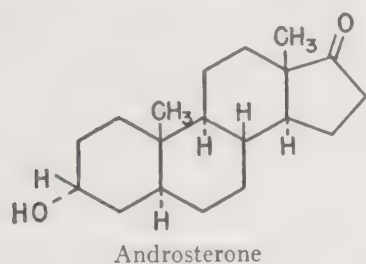
The potency of testosterone and androgenic substances is determined by their ability to promote comb growth in capons or upon their ability to stimulate the growth of the seminal vesicles of castrated male rodents. There is a significant difference in the interpretation of the results obtained by these two assay methods. For example, when castrated rats were treated with

amounts of urinary and testicular extracts of equivalent potency in terms of capon units, the average weights of the seminal vesicles of the controls of the animals receiving urinary extracts and those receiving testicular extracts were in the ratio of 1:14:67.

The basic function⁴⁷ of the male sex hormone testosterone is to induce normal development of the male reproductive tract and to maintain the secondary male sex characteristics and behavior patterns. It plays a role in the development of the penis, the seminal vesicles, the prostate gland and in the descent of the testes. The accessory characteristics affected are depth of voice.

distribution of facial and body hair and male type of skeletal muscular development. Muscular strength and endurance are measurably increased with the administration of the male hormone. Testosterone confers a sense of "well-being" and restores mental equilibrium and energy. It also can measurably increase the resistancy of the central nervous system to fatigue. Testosterone has slight corticometric activity.

It follows that testosterone therapy is indicated to bring about a normal state in cases where a deficiency of this hormone is known. Such conditions are sexual infantilism in the male, male climacteric, etc.



Testosterone has been used in females to treat certain ovarian dysfunctions such as menorrhagia and dysmenorrhea. It also has been used to suppress lactation and in treatment of breast engorgement.

Testosterone is inactive orally and must be administered intramuscularly. In the latter case, it is absorbed quite rapidly. It is thought to be inactivated in the intestinal tract by the bacteria that are present; they

possibly convert it to feebly active compounds.

Testosterone is converted in the body and excreted in the urine as androsterone, dehydroisoandrosterone and isoandrosterone. Androsterone is 1/7 to 1/10 as active as testosterone, and dehydroisoandrosterone and isoandrosterone are 1/20 as active as testosterone. It is interesting to note the marked difference in the physiologic activity of these two compounds that differ only in the spacial configuration of the hydrogen and hydroxyl group at C₃.

The following relationships in structure to activity in this series has been established.⁴⁸

COMPOUND	MICROGAMS EQUIVALENT TO AN INTERNATIONAL UNIT
Testosterone	15
17 α -acetate	20
Dihydrotestosterone	
17 α -trans	20
17 Cis	300
Androsterone	
Cis-3-(α)-17 α -keto	100
Trans-3-(β)-17 α -keto ..	300
Androstanedione-3,17	130
Androstenediol-3,17	
3(β),-17(α)	500
3(β),-17(β)	800-1000
3 α -Hydroxyetiocholanone-17	inert
3 β -Hydroxyetiocholanone-17	inert

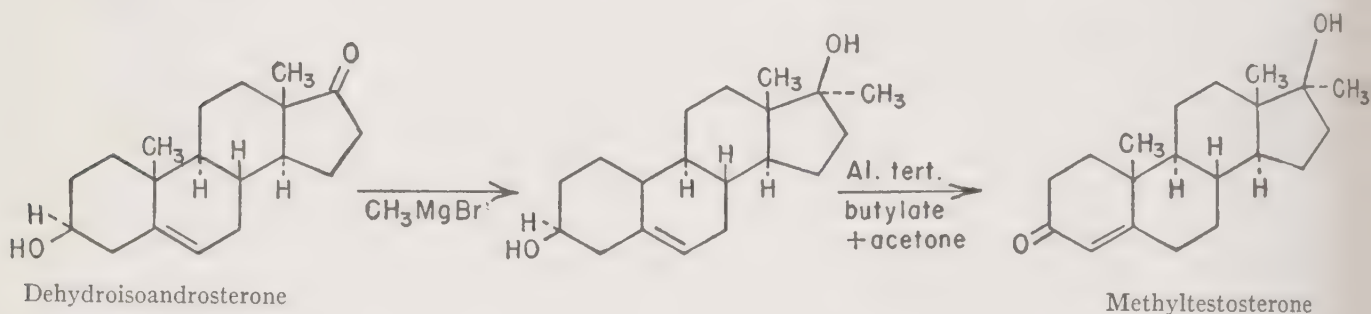
It becomes apparent, from a study of the above structures when correlated with their activities, that for maximum activity rings A and B must be trans, the OH group at C₁₇ must be α - and the presence of a ketone group at C₃ is required. The double bond originally present in testosterone apparently contributes very little to the activity. The trans fusion of rings A and B contributes greatly to the activity.

Testosterone Propionate U.S.P. is prepared by esterifying the OH at C₁₇ with propionic acid. It occurs as white or slightly yellow crystals or as a crystalline powder that is odorless and stable in air. It is insoluble in water, freely soluble in alcohol, ether and other organic solvents, and is soluble in vegetable oils. It is sensitive to alkali, a property of the C₃ ketone conjugated with the double bond.

Testosterone is used as the propionate to prolong its activity when injected intramuscularly. It is weakly active orally. Esterification of testosterone does not affect its activity.

The average dose (intramuscular) is 25 mg.

Methyl Testosterone U.S.P. is 17-methyl- Δ^4 -androstene-17-(α)-ol-3-one. It is prepared from dehydroisoandrosterone as follows:



Methyl testosterone occurs as white or slightly yellow crystals or as a crystalline powder that is odorless and stable in air but is affected by light. It is insoluble in water, soluble in alcohol, ether and other organic solvents, and sparingly soluble in vegetable oils. It is sensitive to alkali.

Methyl testosterone possesses the same action as testosterone; however, it is orally active. Apparently one of the points of attack by intestinal bacteria to inactivate testosterone is the OH group at C₁₇. The small methyl group replacing the hydrogen prevents this attack, but the stereochemical specificity has not been sufficiently altered to prevent it from possessing a relative high androgenic activity. Methyl testosterone has a more pronounced corticometric activity.

It may be used orally, sublingually or topically.

The average doses are oral, 10 mg. and sublingual, 5 mg.

ADRENAL CORTEX HORMONES

It has long been known that adrenalectomy in the experimental animal will cause death in a few days. It has also been known

for some time that suitable extracts of the adrenal cortex will prolong or prevent death in adrenalectomized animals. Thomas Addison, in 1855, described a syndrome, now usually known as Addison's disease, which is caused by diminished adrenal cortex activity that, for example, may be due to a disease such as tuberculosis of the adrenal gland, adrenal tumors, etc. Addison's disease is characterized by extreme weakness,

anorexia, anemia, nausea and vomiting, pigmentation of the skin, low blood pressure and mental depression.

The most important deficiency symptoms which follow adrenalectomy and which are susceptible to quantitative estimations are: (1) disturbance of the Na⁺, K⁺, Cl⁻ and water balance (increases excretion of Na⁺, Cl⁻ and water; retention of K⁺), (2) increase of the urea content of the blood, (3) asthenia (inefficiency of muscle), (4) disturbance of carbohydrate metabolism (decrease in liver glycogen, decreased resistance to insulin) and (5) reductions of resistance to various traumata (cold, mechanical or chemical shock).

Most methods of assay depend on the alleviation of such deficiency symptoms in adrenalectomized animals. Some, however, make use of normal animals. A properly prepared adrenal cortex extract, when administered to an adrenalectomized animal, will abolish the above symptoms.

Twenty-eight crystalline steroids,⁴⁹ plus a biologically active amorphous fraction, have been shown to be present in adrenal cortex extracts. These principles were first

known as cortin. Of the crystalline steroids (see Table 43), 6 give varying degrees of relief in adrenal cortical insufficiency. The amorphous fraction represents about 50 per cent of the activity of the adrenal cortex and is about 2.5 to 5 times as active as the most active crystalline compound. See the following table:

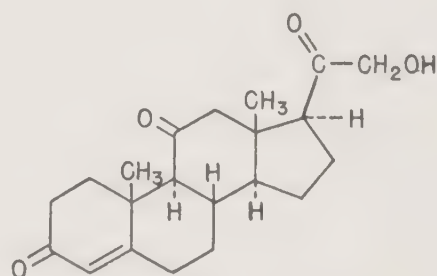
COMPOUND	AMOUNT (MG./DAY) TO MAINTAIN A 20 KG. ADRENALECTOMIZED DOG	RATIO
Amorphous fraction (Wintersteiner & Pfiffner).....	0.045	1
Amorphous fraction (Mason; Kendall).....	0.02 - 0.04	0.5 - 1
Desoxycorticosterone acetate	0.1	2.5
Desoxycorticosterone	0.3	7.5
Corticosterone	2.0	50.0
17-Hydroxy-11-dehydrocorticosterone	7 - 11	250.0

Table 43 (page 410) gives a comparison of the six active, crystalline adrenal cortex hormones together with that of the amorphous fraction when assayed by several standard tests.

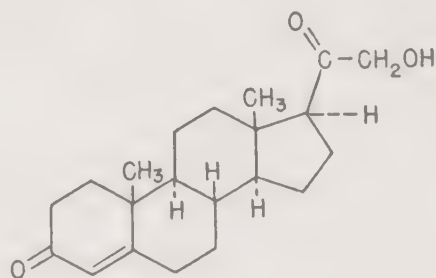
The data recorded in columns A to D indicate that the activities of the crystalline compounds decrease with an increase in the oxygen content. The amorphous fraction, which has a high oxygen content, shows a uniform high degree of activity. The reverse of the above relationships for the crystalline compounds is true for columns E to G, whereas the amorphous fraction exhibits little if any activity in these tests.

It becomes apparent from a study of this table that one crystalline compound, i. e., corticosterone, is effective in all the tests even though it may not be as active as some others, such as desoxycorticosterone and its acetate and the amorphous fraction in certain specific tests.

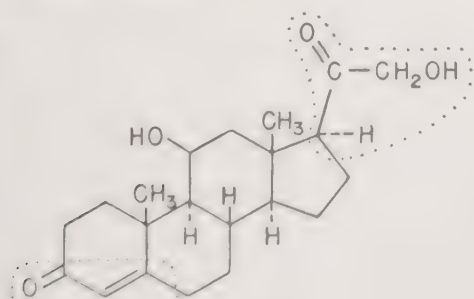
The two structures encircled with a dotted line are essential for all known activity and are apparently the only ones necessary for the control of the salt balance. The C_{11} —OH is essential for carbohydrate activity, which is enhanced if an OH is also present at C_{17} .⁵³



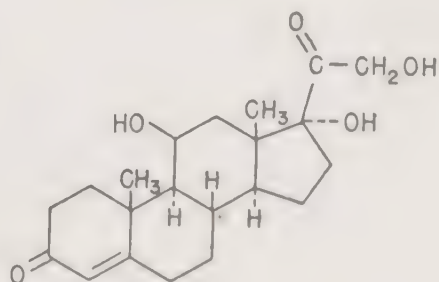
11-Dehydrocorticosterone



Desoxycorticosterone



Corticosterone



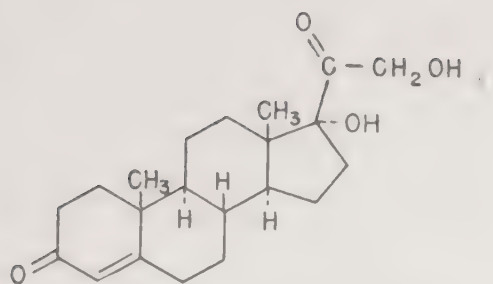
17-Hydroxycorticosterone

TABLE 43. COMPARISON OF ACTIVITY OF THE SIX, ACTIVE, CRYSTALLINE ADRENAL CORTEX HORMONES (AND ALSO AMORPHOUS FRACTION)

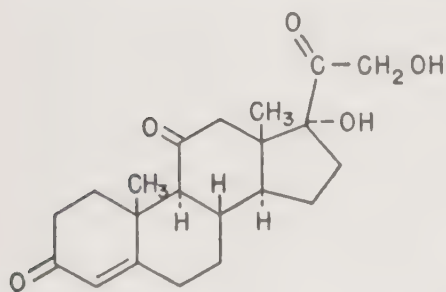
SUBSTANCE	GROUP	A. SURVIVAL TEST IN RATS ⁵⁰	B. TEST IN ADRENAL- ECTOMIZED DOGS ⁵⁰	C. NA + AND RETENTION IN NORMAL DOGS	D. EVERSE-DE FREMY TEST ⁵¹ (MUSCULAR EFFICIENCY)	E. INGLE'S TEST ⁵²	F. DIBETO- GENIC ACTION	G. ANTI- INSULIN TEST
Desoxycorticosterone	C ₂₁ O ₃	+	+	+	+	+	0	0
Desoxycorticosterone Acetate	C ₂₁ O ₃	+	+	+	+	+	0	0
Corticosterone	C ₂₁ O ₄	+	+	+	+	+	+	+
11-Dehydrocorticosterone	C ₂₁ O ₄	+	+	+	?	+	+	+
17-Hydroxy-11-desoxycorti- costerone	C ₂₁ O ₄	+	?	?	+	+	?	0
17-Hydroxycorticosterone	C ₂₁ O ₃	+	+	—	+	+	+	+
17-Hydroxy-11-dehydrocorti- costerone	C ₂₁ O ₅	+	+	—	+	+	+	+
Amorphous fraction	C ₂₁ O ₅ (?)	+	+	+(?)	+	+	0(?)	?

+ = Activity.

— = Negative Na⁺ and ⁻ retention,
i.e., increased excretion.



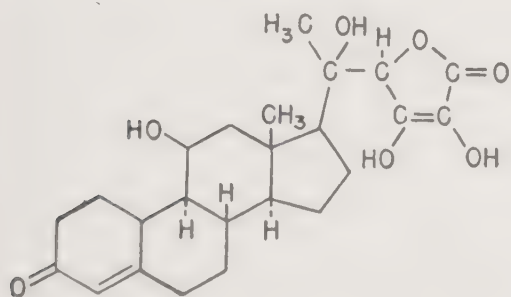
17-Hydroxy-11-dehydrocorticosterone



17-Hydroxy-11-desoxycorticosterone

11-Dehydro-17-hydroxycorticosterone is three times as active as 11-dehydrocorticosterone when tested for its glycogen deposition activity in adrenalectomized mice. 11-Dehydro-17-hydroxycorticosterone is 12 times as active as corticosterone and 13 times as active as 11-desoxycorticosterone when used in the cold test employing adrenalectomized rats.⁵⁴

A new active steroid that has the following structure has been isolated from the water-soluble portion of adrenal cortex extracts.

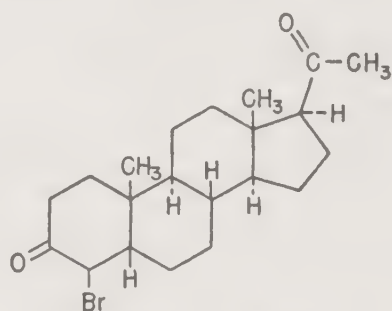


This compound was claimed to be as active or more active than desoxycorticosterone in life maintenance tests and to have carbohydrate activity similar to that of dehydrocorticosterone.⁵⁵

The influence on carbohydrate activity or

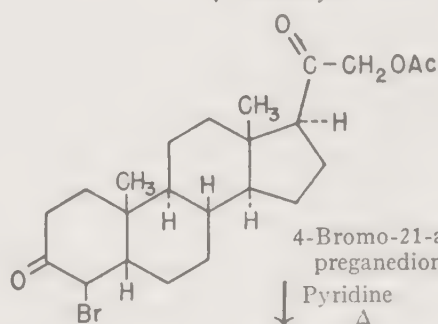
metabolism is not completely specific since the physiologically potent cardiac glycosides, strophanthidin, ouabain and digitalin, of which the former and the latter certainly do not have an oxygen at C₁₁, are able in small doses to lengthen the life of adrenalectomized rats. In addition, they also exhibit some anti-insulin activity.

Desoxycorticosterone Acetate (Deoxycostone Acetate) U.S.P. (Percorten, Cortate) is 11-desoxycorticosterone or the acetate of Δ^4 -pregnene-21-ol-3:20-dione. It cannot be isolated in commercial quantities from adrenal cortex extracts. It is synthesized commercially from one of the intermediates obtained from cholesterol, stigmasterol⁵⁶ or the sapogenins⁵⁷ when they are used for the synthesis of testosterone and progesterone.



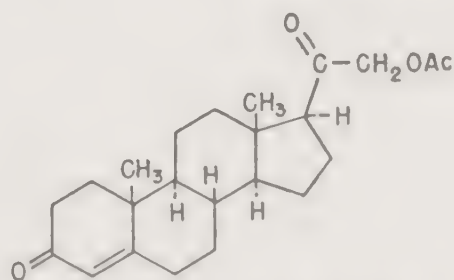
4-Bromopregnanedione-3,20

AcOH
Persulfuric Acid
7-10 days



4-Bromo-21-acetoxypregnanedione-3,20

Pyridine
 Δ



Desoxycorticosterone Acetate

Desoxycorticosterone acetate occurs as a white, crystalline powder, odorless and stable in air. It is practically insoluble in water, sparingly soluble in alcohol or acetone, and slightly soluble in vegetable oils.

The acetate group at C₂₁ is so unstable that it can be saponified readily by means of potassium bicarbonate. Desoxycorticosterone is very unstable in alkali and is very readily oxidized, as is evidenced by the fact that it will reduce Tollen's reagent in the cold. It should be stored in well-closed, light-resistant containers.

Desoxycorticosterone acetate is about 3 times as active as the free compound because, when administered by intramuscular injection or crystal implantation, it is more slowly absorbed and apparently less readily altered by the body to inactive products.

The physiologic activity of desoxycorticosterone has been described previously. It is used in 5 mg. daily doses to as much as 10 mg. every 4 hours in order to control the disordered blood electrolyte balance⁵⁸ resulting from tissue destruction in burns and, thus, to prevent the development of late shock as indicated by the extent of burning, hemoconcentration and clinical signs of impending shock. It also can be used in Addison's disease when accompanied by liberal salt and water intake. It is useful in surgical shock both pre- and postoperatively.

Desoxycorticosterone activity differs from that of extracts of the adrenal cortex in being chiefly concerned with salt and water metabolism.

Adrenal Cortex Extract N.N.R. is an extract of adrenal glands, from domesticated animals used as food in man, containing the cortical steroids essential for the maintenance of life in adrenalectomized animals.

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26

Plant Alkaloids

PYRIDINE GROUP

PEPPER AND PEPPER ALKALOIDS

ARECA NUT AND ARECA NUT

ALKALOIDS

CONIUM AND CONIUM ALKALOIDS

POMEGRANATE AND POMEGRANATE

ALKALOIDS

LOBELIA AND LOBELIA ALKALOIDS

TOBACCO AND TOBACCO ALKALOIDS

TROPANE GROUP

SOLANACEOUS ALKALOIDS

COCA AND THE COCA ALKALOIDS

LUPINANE GROUP

ISOQUINOLINE GROUP

CACTUS AND ITS ALKALOIDS

HYDRASTIS AND HYDRASTIS ALKALOIDS

PAPAVERACEOUS ALKALOIDS

IPECAC AND THE IPECAC ALKALOIDS

CURARE AND CURARE ALKALOIDS

QUINOLINE GROUP

CINCHONA AND THE CINCHONA

ALKALOIDS

CUPREA BARK ALKALOIDS

INDOLE GROUP

YOHIMBE AND THE YOHIMBE ALKALOIDS

ERGOT AND THE ERGOT ALKALOIDS

CALABAR BEAN AND ITS ALKALOIDS

NUX VOMICA AND THE NUX VOMICA

ALKALOIDS

GLYOXALINE GROUP

PILOCARPUS AND THE PILOCARPUS

ALKALOIDS

ALKALOIDAL AMINES

EPHEDRA AND EPHEDRINE

COLCHICUM AND ITS ALKALOIDS

PURINE GROUP

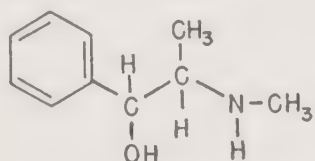
Alkaloids are a naturally occurring group of compounds characterized by the omnipresence of nitrogen and yet being structurally unrelated in many instances. Many alkaloids possess physiologic activity, but some are almost devoid of activity. Thus, the grouping of these compounds was not arrived at on a strictly chemical or pharmacologic basis, but rather on a traditional basis by which those natural products which exhibited basic properties* (i.e., salt for-

mation with acids) were considered as a group set apart from other natural products not exhibiting this property. The name "alkaloid" is derived from the fact that the compounds, in general, behave similarly to the alkali bases (e.g., NaOH) in that they neutralize acids. Thus, early workers coined the term alkaloid from *alkali* and *oid* (meaning like), or literally "alkali-like."

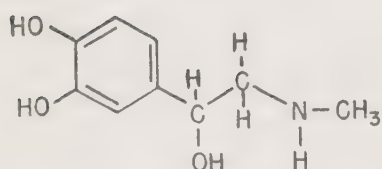
It is customary to consider alkaloids as being of plant origin, although there are nitrogenous substances derived from animal sources that also exhibit basic properties.

* Sometimes the compound requires hydrolysis to bring out the basic properties, e.g., piperine.

Indeed, in a few cases there is only a minor difference between the plant alkaloid and the basic substance of animal origin as evidenced by ephedrine (plant) and epinephrine (animal). In this text, however, only those nitrogenous bases derived from vegetable sources will be considered as alkaloids.



Ephedrine



Epinephrine

Alkaloids are not named systematically, as becomes readily apparent from a perusal of the various alkaloidal names. The only uniformity in the nomenclature of alkaloids arises from the universal ending "*ine*", which serves to distinguish them from other plant products, particularly the glycosides which end in "*in*." In general, the names are derived from one of the following sources: names of plants (atropine), physiologic action (morphine), physical properties (hygrine) or, rarely, the name of an investigator (pelletierine). Use is made of suffixes and especially prefixes to distinguish between individual alkaloids found in the same plant. Some of the prefixes in common use are *iso*, *pseudo*, *neo*, *epi*, etc. Occasionally, the prefix has a particular significance attached to it, as in the case of the prefix *nor*. Originally, *nor* was prefixed to the existing name of the alkaloid to indicate that the *nor* compound was N-demethylated as compared to the original compound which carried a methyl group on the nitrogen. This meaning has been extended to include also those alkaloids in which a methoxyl group is demethylated, resulting in a *nor* compound.

Of the two major classifications of plants,

the Phanerogams (flowering plants) and Cryptogams (nonflowering plants), the former (particularly among the dicotyledons) possesses by far the greater number of alkaloid-containing plants. While the presence of alkaloids is not confined to any particular family, certain families are much richer than others in alkaloidal plants, namely, the *Papaveraceae*, *Solanaceae*, *Leguminosae*, *Ranunculaceae*, *Rubiaceae*, *Apocynaceae* and *Fumariaceae*. The existence of a single alkaloid in a plant is not common. Usually, there is a group of structurally related alkaloids occurring in the same plant. The existence of a certain alkaloid in a plant, however, does not preclude its presence in others, as evidenced by the occurrence of sparteine, berberine and protopine in a number of different plants not necessarily belonging to the same family. In general, however, alkaloids are specific for certain related plants and are not found in others.

The alkaloidal content is often concentrated in some specific plant part, e.g., root, bark, rhizome, although sometimes it is disseminated throughout the entire plant. Alkaloids, because of their basic character, normally exist in plant tissue in the form of salts of various acids. The acids may be inorganic (e.g., sulfuric and phosphoric) or organic (e.g., lactic and malic). Sometimes the organic acid is a specific one such as aconitic acid which occurs in combination with the alkaloid aconitine or meconic acid, occurring with the opium alkaloids.

The time of year when plants are collected has an important bearing on the alkaloidal content. In some plants the content may be greatest when the seeds are ripe, whereas in others it may be greatest in an immature stage. It has been rather convincingly demonstrated, especially in the case of cinchona, belladonna, opium and ephedra, that cultivation of alkaloid-containing plants will often result in a significant increase in the alkaloid content.

Most alkaloids occur as odorless, well-crystallized, colorless compounds, although

oxygen-free alkaloids are usually liquid, e.g., coniine and nicotine. Only a few colored alkaloids are known, of which the salts of berberine and sanguinarine are typical. Alkaloids usually form crystalline salts with acids and, in general, the salts are water-soluble but insoluble in immiscible solvents such as ether and chloroform, whereas the free alkaloid is water-insoluble* but soluble in immiscible solvents. Optical activity is very often associated with alkaloids and their salts, the optical activity (i.e., specific rotation) varying with the solvent used, the temperature, the wave length of light and other minor factors.

The nitrogen which is an essential constituent of all alkaloids accounts for much of the chemical reactivity of these bases. The nitrogen is usually present in the tertiary form, less often as the secondary and rarely as a primary amine. When it occurs in the secondary or tertiary form, it usually constitutes a part of a ring system. Tertiary nitrogens in which only two of the bonds are involved in a ring usually have methyl as the third substituent, i.e., as an N-methyl group. Thus far, methyl appears to be the only alkyl group which has been found substituted on nitrogen, and it is also true that alkoxyl groups that may be present are invariably present as methoxyl or methylenedioxy groups.

As pointed out previously, the nitrogen is usually basic and, therefore, is reactive. The nitrogen basicity is responsible for the fact that alkaloids can be precipitated by various reagents and also for their ability to form salts with both inorganic and organic acids.

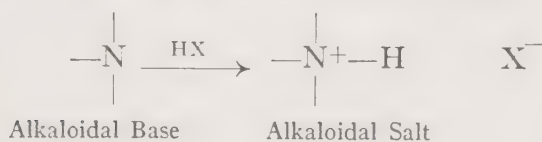
Because alkaloids react with various reagents to form insoluble precipitates, these reagents have been used to test for the presence of alkaloids in plants and plant extracts. A dilute acid extract of a plant can be used for the detection of alkaloids. The pres-

ence of alkaloids is indicated by the formation of a precipitate when a few drops of reagent are added to the acid extract. However, other plant constituents such as proteins, glycosides and amino acids may give a false positive test. If no precipitate is obtained, it is highly possible that alkaloids are absent. To eliminate the possibility of a false test, the acid solution may be alkalized and extracted with an immiscible solvent. The extracted material, from which the solvent has been removed, is dissolved in a small amount of acid and tested as before with the alkaloidal reagent. If the test is again positive, the possibility exists that an alkaloid is present. Some of the common alkaloidal precipitating agents are mercuric iodide test solution (Valser's), mercuric-potassium iodide test solution (Mayer's), potassium triiodide (Wagner's), phosphomolybdic acid (Sonnenschein's), phosphotungstic acid (Scheibler's), silicotungstic acid (Bertrand's) and tannic acid test solution. A few alkaloidal precipitants, such as chlorauric acid (HAuCl_4) and chloroplatinic acid (H_2PtCl_6), will react with certain alkaloids (e.g., cocaine) to form crystalline salts of a characteristic shape and composition. Occasionally, it is possible to identify alkaloids on the basis of the crystal shape of these salts. In addition, because these salts are definite in composition, they may be used for analytical purposes to determine the formula of unknown alkaloids. In passing, it should be mentioned that there are various color tests applied to alkaloids. These tests usually depend upon dehydration or oxidation of the alkaloid, with a resultant characteristic color. Some of the common reagents are formaldehyde, nitric acid, potassium permanganate and potassium dichromate.

As previously observed, alkaloids react with acids, both organic and inorganic, to form salts. It is, of course, obvious that the anion of the acid is still capable of reacting in a normal way with the usual qualitative reagents used to test for it since it is in an ionic form. For example, chloride ion reacts

* This is not a rigid requirement, since some important alkaloids (e.g., ephedrine and ergonovine) are known which are water-soluble.

readily with silver ion to form insoluble silver chloride. This is a common incompatibility of alkaloidal hydrochlorides with soluble silver salts, e.g., silver nitrate. The same, of course, holds true for the anions of alkaloidal sulfates, phosphates, etc. when in the presence of precipitating reagents. Because salts of alkaloids are usually well-crystallized and possess definite melting points, they are often used to characterize the alkaloids. In fact, they are the usual form in which the alkaloid is marketed because of their stability and solubility in water. The choice of acid depends a great deal upon the ease of crystallization of the resultant salt and its stability and solubility. Furthermore, it is sometimes found that certain salts of an alkaloid show greater activity or less toxicity than other salts of the same alkaloid.

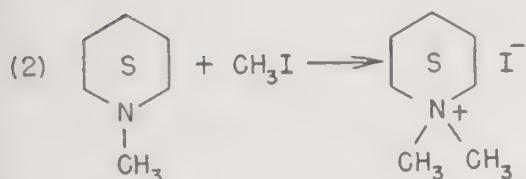
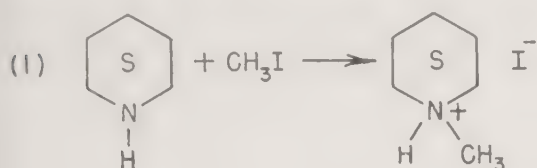


The fact that alkaloids are usually insoluble in water, whereas the salts are soluble in water, is made use of in the isolation of alkaloids. A usual procedure, although by no means the only one, is to extract the plant material in a suitable state of comminution with a slightly acidified alcoholic solution which extracts the alkaloids as water- and alcohol-soluble salts. This alcoholic solution is evaporated to remove the alcohol, leaving an aqueous solution which may be diluted to a convenient volume with water. The diluted aqueous solution then is alkalinized (e.g., with alkali carbonates or hydroxides) to liberate the free alkaloids, which are extracted from the aqueous medium with a suitable immiscible solvent. In this manner a partial purification is effected. To further purify the alkaloids they may be removed from the immiscible solvent by extraction in a separatory funnel with a dilute acid, which in turn is extracted, after alkalinization, with the immiscible solvent. Removal of the solvent by distillation leaves an alkaloidal resi-

due which may or may not be a mixture of alkaloids. The separation of a mixture of alkaloids often presents a problem challenging the best efforts of the pharmaceutical chemist. Usually, attempts are made to crystallize the constituent alkaloids from one another as their salts, or in the case of liquid alkaloids, resort may be had to distillation technics. In many cases it is possible to effect separation by making use of chemical reactivities, other than that of nitrogen reactivity, inherent in the individual molecules. For example, phenolic and nonphenolic alkaloids may be separated by the proper use of sodium hydroxide and sodium carbonate. The separation is dependent upon the fact that a base containing a phenolic hydroxyl, being weakly acidic, will not react with sodium carbonate but will readily form a water-soluble sodium salt with sodium hydroxide. Thus, considering an acid solution of the mixed alkaloids as a starting point, it is alkalinized with a concentrated solution of sodium hydroxide. This effects a liberation of the nonphenolic component as the free base. This may be extracted from the alkaline medium with a suitable immiscible solvent. The residual alkaline liquid, containing the phenolic alkaloids, then is acidified and realkalinized with sodium carbonate to liberate the phenolic alkaloids as free bases. These are extracted from the alkaline solution with a suitable immiscible solvent. Further separation of the individual phenolic and nonphenolic alkaloids would be accomplished by other technics. Occasionally, it is possible to effect partial separation by utilizing the reactivity of a carbonyl group. In this case, the success of the separation depends largely on changing the properties of the alkaloid or alkaloids containing the reactive group by converting it to some derivative. It is essential that the original alkaloid be easily recoverable from a derivative of this type.

A typical reaction of many alkaloids is with alkyl halides, particularly with methyl iodide. Secondary amines react to give the

hydriodide of an N-methylated derivative of the alkaloid (1). Tertiary amines react irreversibly to give methiodides (2). Meth-



iodides are derivatives of a group of nitrogenous compounds known as "quaternary bases" (q.v.). Quaternary bases and their salts occur infrequently among the alkaloids (see however, *d*-tubocurarine chloride). Methiodides are of importance in characterizing alkaloids because they are often crystalline. They are also an important tool for the chemist in determining alkaloidal structures, the process wherein they are used being termed "exhaustive methylation." Exhaustive methylation, in general, consists of fully methylating the nitrogen (primary, secondary or tertiary) and then cleaving the nitrogen-carbon bond by heat or reduction. If heat is used as a cleaving agent, the products will be an olefin and trimethylamine, whereas if reduction is employed, the products will be trimethylamine and a saturated hydrocarbon. For a more extended discussion of the uses and limitations of this and related reactions employed in structural work the student is referred to more exhaustive works.

Alkaloids have been classified in a number of different ways, depending upon the viewpoint of the worker classifying them. In this text, the classification of Henry will be used with some modification.

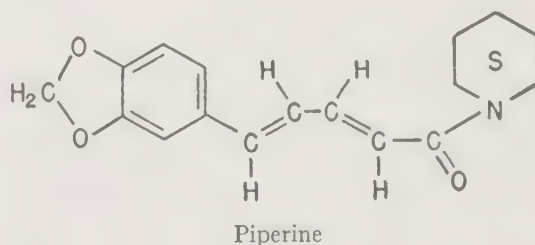
PYRIDINE GROUP

PEPPER AND PEPPER ALKALOIDS

There are several species of pepper, of which *Piper nigrum* is the most important.

It supplies the white and black peppers which are familiar as spices. Black pepper, which was official in the N.F.VI, is composed of the dried, unripe fruit of the plant, whereas white pepper is the decorticated ripe fruit of the same plant. The chief alkaloidal constituents of pepper are piperine and chavicine. The crude drug, although primarily a spice, has been used for its carminative and local irritant properties.

Piperine. Piperine, which was formerly official in the U.S.P. VIII, is piperoyl piperide. It occurs naturally in various pepper species, the most important of which is *Piper nigrum* (5 to 9 per cent piperine). It originally was thought to be the principal constituent which imparted the characteristic pungent taste to pepper. However, it is probable that an isomer, chavicine, is primarily responsible for the taste.



Piperine occurs as colorless, odorless, monoclinic needles or prisms. It has a somewhat burning taste which becomes more intense the longer the material remains in contact with the tongue. It is almost insoluble in water but soluble in alcohol (1:15), chloroform (1:1.7) or ether (1:36).*

Piperine, being an amide, exhibits only a very weak basicity and is incapable of forming stable salts. It is easily hydrolyzed with alcoholic potash to yield piperidine and piperic acid.

The alkaloid is obtained from pepper by extraction with alcohol, the residue of the alcoholic extract being digested with alkali to saponify the resins. The resin-free ma-

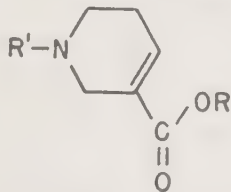
* In this chapter a solubility expressed as (1:15) indicates that 1 Gm. is soluble in 15 cc. of the solvent at 25° C. Solubilities at other temperatures will be so indicated.

terial then is recrystallized from alcohol to give monoclinic needles.

Although at one time piperine was thought to possess antiperiodic properties, this has never been proven, and it is little used medicinally.

ARECA NUT AND ARECA NUT ALKALOIDS

The areca or betel nut (seed of *Areca Catechu*) yields arecoline together with several constitutionally similar alkaloids, namely, arecaidine, guvacine and guvacoline. The alkaloids of the areca nut may all be considered to be derivatives of guvacine (Δ^3 -tetrahydropyridine-3-carboxylic acid). The following table shows the interrelationships.

BASIC STRUCTURE	GUVACINE	GUVACOLINE	ARECAIDINE	ARECOLINE
	R = H	R = CH ₃	R = H	R = CH ₃
	R' = H	R' = H	R' = CH ₃	R' = CH ₃

When mixed with lime and betel leaves, the seeds are chewed extensively in the Far East. Used in this manner, the drug creates a pleasant contentment, but is exceedingly habit forming. In humans, crude, ground areca nuts have been used as a vermifuge in China and India. On the Continent and in this country, the crude drug, as well as its constituents, is used almost exclusively in veterinary practice as a laxative and anthelmintic.

Arecoline Hydrobromide N.F. Arecoline is the methyl ester of N-methyl guvacine and is the principal alkaloid obtained from the areca nut. It occurs in the nut to the extent of 0.1 to 0.4 per cent. The N.F. requires that official areca nut contain at least 0.35 per cent of ether-soluble alkaloids calculated as arecoline.

Arecoline may be obtained directly from the seeds or it may be prepared synthetically in a number of ways. The method of Dan-

kova¹ is the most recent and utilizes ethylene oxide as a starting material. Ethylene oxide is converted successively to the chlorohydrin, cyanohydrin, β -chloropropionic acid and then to the ethyl ester of the acid. The ethyl ester then is converted to arecoline by the series of reactions shown at the top of page 421.

The free base is a colorless, odorless, strongly basic, optically inactive, water-miscible liquid. It readily forms salts, but these are usually deliquescent. The hydrobromide, which is practically non-deliquescent, is the form in which arecoline is recognized officially. It occurs as a white, finely crystalline powder possessing a bitter taste. Because it

is affected by light, it should be stored in tight, light-resistant containers.

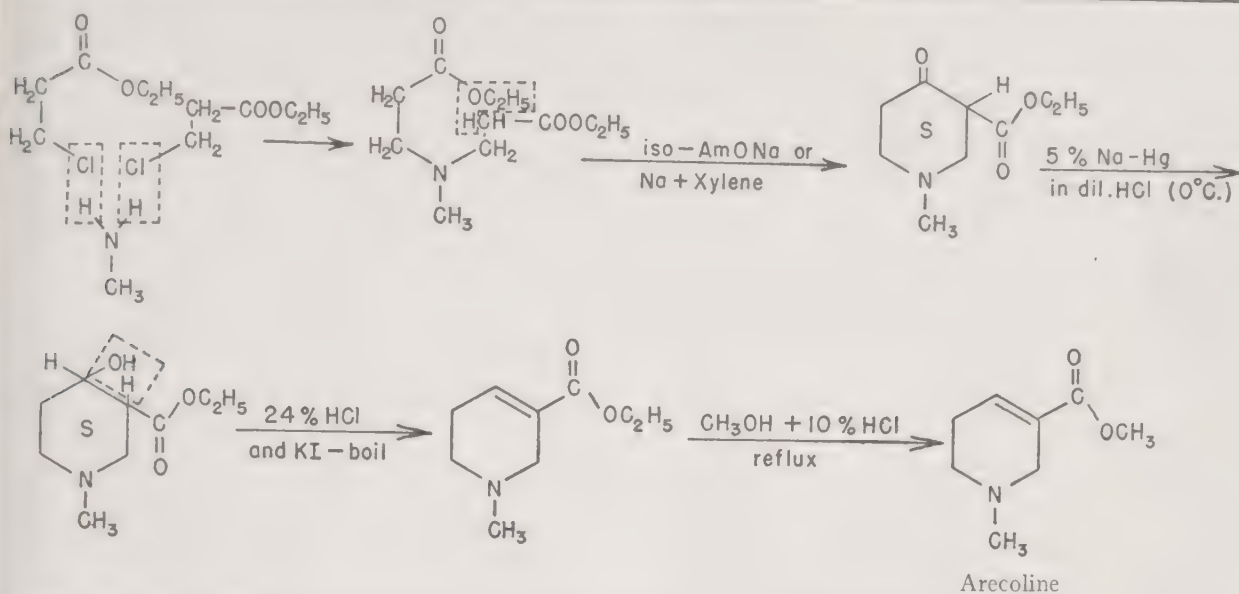
One gram of the hydrobromide dissolves in approximately 1 cc. of water or 10 cc. of alcohol at 25° C. and in about 2 cc. of boiling alcohol. It is only slightly soluble in chloroform or ether. Aqueous solutions of the hydrobromide are practically neutral.

The salt is used exclusively in veterinary practice as an anthelmintic, cathartic and miotic. Its anthelmintic (principally taenia-fuge) and cathartic effects are due to the strong peristalsis which it induces. Miotic effects in iritis are obtainable by instillation of a 0.5 to 1 per cent solution in the eye.

The average dose is: for horses, 30 mg. subcutaneously; for dogs, 1.5 mg. per Kg. orally.

CONIUM AND CONIUM ALKALOIDS

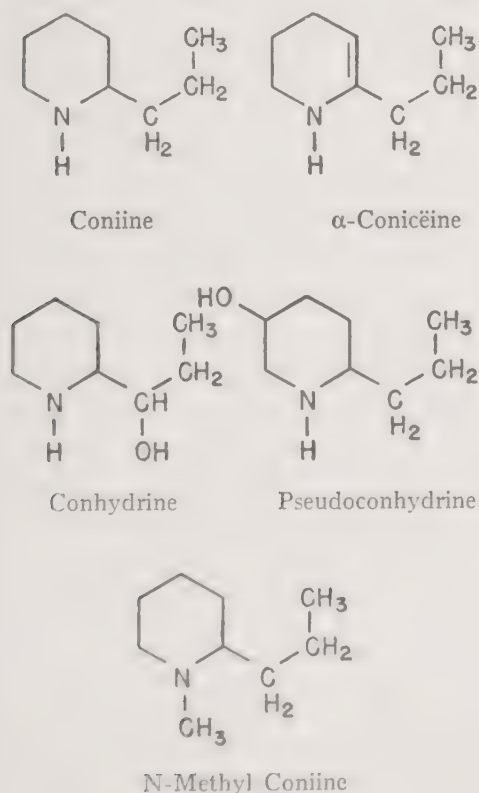
Hemlock, which is commonly known as Poison Hemlock, Spotted Cowbane or Poison



Parsley, was formerly official as *Conium Fruit* (N.F. V) and is derived from *Conium maculatum*. This poisonous plant owes its toxic properties to the presence of several alkaloids, namely coniine, γ -coniceine, conhydrine, pseudoconhydrine and N-methyl coniine, of which coniine is the most important. The unripe, fully grown, dried fruit yields approximately 0.5 to 1.5 per cent of

coniine. By a comparison of the formulae, the close structural resemblance existing among these alkaloids can be appreciated. They are toxic, paralyzing the motor nerve terminations, and death results from respiratory paralysis. Because of this toxicity, poison hemlock was used by the ancient Greeks as a death penalty (e.g., Socrates, 399 B.C.). The toxicity of the individual alkaloids varies with the structure, however. The toxicity of γ -coniceine is 18 times that of coniine, but the hydroxylated coniines (conhydrines) are much less toxic than coniine. The *d*- and *l*-forms of coniine are identical in activity. Conium fruit was formerly used for its sedative and narcotic actions but, due to the unpredictability of action of its galenical preparations as well as of the drug itself, its use has been largely discontinued.

Coniine. Chemically, coniine is the dextrogyrate form of α -*n*-propyl piperidine. It is one of the few liquid alkaloids. Above -2° C. it exists as a colorless, oily liquid possessing a penetrating odor, a burning taste and strongly basic properties. At room temperature, the free base is only slightly soluble in water (1:90) but, oddly enough, it dissolves about 25 per cent of water at that temperature. It is readily miscible with alcohol and is soluble in most organic solvents. It forms



well-crystallized salts such as the hydrochloride and hydrobromide, these being the usual forms in which it is used medicinally. It darkens on exposure to light.

The alkaloid, together with its associated alkaloids, may be extracted from the plant by the method of Chemnitz, which is essentially the extraction of the alkalized drug with ether, followed by partitioning between ether and acid. Special procedures are used to remove fat and coloring matter. Final purification is effected by fractionation. The first synthesis of the alkaloid was effected by Ladenburg.² Coniine has the distinction of being the first alkaloid to be prepared synthetically. The credit for the elucidation of the structure of coniine belongs to Hoffmann.

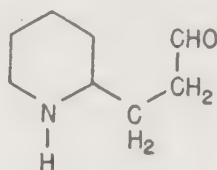
Although the crude drug and the coniine salts were at one time used internally for their sedative and narcotic effects, this use has been largely discontinued. Externally, the coniine salts are incorporated into ointments and infrequently used for their local analgesic action in the symptomatic relief of pruritus ani, hemorrhoids and anal fissures.

POMEGRANATE AND POMEGRANATE ALKALOIDS

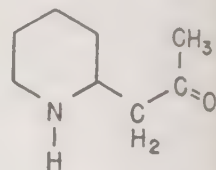
A number of well-defined alkaloids are obtained from the root bark of the pomegranate tree (*Punica granatum*). The alkaloids are found to the extent of 0.5 to 1 per cent and consist of pelletierine, iso-pelletierine, methyl iso-pelletierine and pseudopelletierine. It is worthy of note that, at first glance, pseudopelletierine seems to differ radically from the other alkaloids. Closer inspection, however, reveals that it has essentially the same structure as methyl iso-pelletierine, but exists in a closed ring form instead of an open chain compound. This close relationship has led to much speculation about its possible biochemical significance, but it has not yet been possible to convert methyl iso-pelletierine into pseudopelletierine.

The first investigations of pomegranate

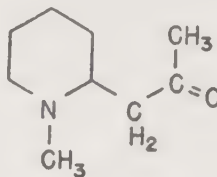
were carried out by Tanret, who isolated most of the alkaloids. His nomenclature has been revised considerably.



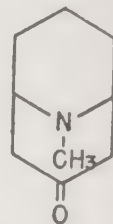
Pelletierine



Iso-pelletierine



Methyl-iso-pelletierine



Pseudopelletierine

The root bark has been used as an anthelmintic, particularly for tapeworm, although it is little used in present-day medicine. Although the crude drug is in disuse, preparations of the alkaloids are still used, e.g., pelletierine tannate.

Pelletierine Tannate N.F. Pelletierine tannate is not a pure salt but is a mixture of the tannates of all the alkaloids in pomegranate bark. The proportion of alkaloids in the mixture is variable. The official requirement is that the alkaloidal tannates, when converted to the hydrochlorides, give a weight of hydrochloride which is at least 20 per cent of the weight of tannate taken. As a consequence, the action of the drug may be variable and is dependent upon the existing proportion of alkaloids in the crude drug.

Pelletierine tannate exists as a light yellow, odorless, amorphous powder which is affected by light. It has an astringent taste. One gram is soluble in 250 cc. of water, and the compound is soluble in alcohol or warm dilute acids. It is only slightly soluble in ether and is insoluble in chloroform.

Alkali decomposes the preparation to yield the free alkaloids. In a saturated aqueous solution the tannic acid portion reacts in the normal manner with ferric chloride to give a blue-black color.

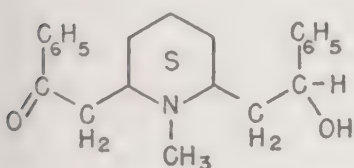
As previously indicated, this preparation is used as a taeniafuge. Its action is to paralyze or kill the tapeworm. It is said to be effective against *Taenia solium* (pork tapeworm), but ineffective against *Hymenolepis nana* (dwarf tapeworm).³ The most pronounced anthelmintic activity is found in pelletierine, which is 10 times more effective than pseudopelletierine. The tannate form of pelletierine is used because it is not very soluble in the stomach and, therefore, is less apt to be absorbed. Administration of the drug, however, is always followed rather closely with a saline cathartic to minimize toxic reactions.

The average dose is 0.25 Gm.

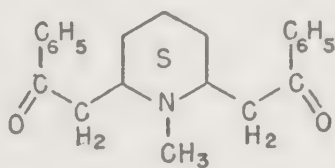
LOBELIA AND LOBELIA ALKALOIDS

The dried leaves and tops of *Lobelia inflata* (Indian tobacco) are official in the N.F. together with a fluid extract and tincture made from the drug.

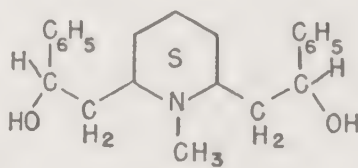
Lobelia inflata contains several alkaloids, chief among which are lobeline, *dl*-lobeline, lobelanine, nor-lobelanine, lobelanidine, nor-lobelanidine, lobinine and isolobinine. Of these, the most important is lobeline, which has been used in therapeutics. The crude drug may contain up to about 0.6 per cent of total alkaloids, of which up to one-half may be lobeline.



Lobeline



Lobelanine



Lobelanidine

The crude drug was used medicinally as a respiratory stimulant for asthma as early as 1785, but has fallen into disuse because of its uncertain action.

Lobeline. This alkaloid is also known as α -lobeline. This is to indicate that it is pure lobeline and not the mixture of bases which until 1921 was known as lobeline.

The alkaloid may be isolated from plant

sources or it may be synthesized by various methods.^{4, 5}

Lobeline occurs as colorless crystals which are levorotatory. It is only sparingly soluble in water or petroleum ether, but is readily soluble in hot alcohol and in the immiscible solvents. Heating and storage of aqueous solutions of lobeline usually causes deterioration and, therefore, when aqueous solutions are prepared they should be used immediately. Slight acidification with hydrochloric acid retards the decomposition. Lobeline forms salts readily, the most common being the hydrochloride and the sulfate. These salts are fairly soluble in water and give aqueous solutions with a slightly acid reaction.

Lobeline possesses a nicotinlike action on the autonomic nervous system, first stimulating and then depressing the ganglia. A curious cross-tolerance exists between nicotine and lobeline, in which animals tolerant to the former also exhibit tolerance to the latter. Based on this phenomenon, a suggested use for lobeline is to aid in breaking the tobacco habit.⁶ Lobeline sulfate is administered orally in 8 mg. doses as often as required to control the withdrawal symptoms, the usual period of treatment being approximately one week. Side reactions, however,

are often worse than letting the withdrawal symptoms run their course.

Use of lobeline as a respiratory stimulant, its principal proposed use, has received an extensive trial. Because its action is somewhat capricious and fleeting, it has not been well received. Its dose in this capacity is 3 to 10 mg. given hypodermically.

TOBACCO AND THE TOBACCO ALKALOIDS

Tobacco (*Nicotiana tabacum*) contains numerous alkaloids, the most important of which is nicotine. The leaf is considered as the usable portion of the plant from a smoking standpoint, although the rest of the plant is valuable for the preparation of nicotine-containing insecticides. The best quality tobacco leaves contain the least amount of nicotine. The chemistry of the various alkaloids of tobacco leaf has been ably reviewed by Jackson,⁷ and a detailed pharmacologic treatment is given by von Oettingen⁸ and others.

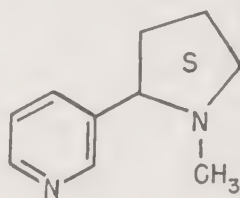
The scientific name of tobacco, *Nicotiana*, is derived from the name of Jean Nicot, the French ambassador to Portugal (ca. 1560) who sent the seeds home to his native land. It was first introduced for purely medicinal purposes, but gradually became a luxury in the form of a smoking or chewing mixture. At the same time, its insecticidal values were noticed. Any medicinal virtues it possesses are greatly overshadowed by its toxicity, which is mainly due to its alkaloidal content. It has, therefore, fallen into disuse as a medicinal agent. Nevertheless, it remains as an important plant because, as stated, it is (1) smoked and (2) used as an insecticide.

The smoking of tobacco leaf has been the subject of many researches designed to show whether it is a harmful or harmless practice. That nicotine is in tobacco smoke is an accepted fact, well illustrated by the nausea and vomiting (principally due to the nicotine) usually associated with the first attempts at smoking by the novice. For a resume of tobacco and its effects in this capacity, the reader is referred to Sollmann.

Because of the toxicity of tobacco, and of nicotine in particular, it has been used as a contact insecticide for sucking insects. Tobacco leaf, with or without added nitrates, when slowly burned in a confined space (e.g., greenhouse), gives off nicotine-containing fumes which are toxic to most plant insects. More or less crude preparations of nicotine

are also used for similar purposes. Typical of these is a 40 per cent aqueous nicotine sulfate solution, commercially known as *Black Leaf "40."* For spraying purposes a solution of the above concentration is highly diluted (1 ounce to 6 gallons of water). Soapy water is used as a diluent to reduce surface tension on the leaf surface. Insects such as aphids, thrips and leaf hoppers thus are easily controlled.

Nicotine. Nicotine is 1-methyl-2-(3-pyridyl)pyrrolidine and is present in tobacco to the extent of 2 to 8 per cent. It exists in the leaf in combination with acetic, malic and citric acids. It was first isolated by Vauquelin from tobacco smoke in 1809; it was characterized by Posselt and Reimann in 1828 and synthesized by Pictet and Rotschy in 1904.



The alkaloid usually is isolated by making an aqueous extract of the powdered plant, alkalinizing the extract and finally steam-distilling the alkaloid from the mixture. Other methods are also in use.^{9,10} Synthesis of the alkaloid is of little interest commercially since nicotine may be obtained very economically from natural sources (tobacco refuse). The principal value of synthesis has been to confirm the postulated structure of the alkaloid.

The free base is a levogyrate, colorless, oily liquid which turns brown on exposure to air and develops a tobacco-like odor. It has a burning taste and an odor similar to that of pyridine. It is miscible with water below 60° C. and is soluble in alcohol and in the immiscible solvents.

It possesses two basic nitrogens and, therefore, unites with two molecules of monobasic acid or alkyl iodide. The weaker basic nitrogen is in the pyridine residue. Numerous salts are known, among which are the hydrochloride, salicylate and tartrate. The tartrate is said to be superior to the others because of its greater solubility and stability.

Because of its toxicity, nicotine is little

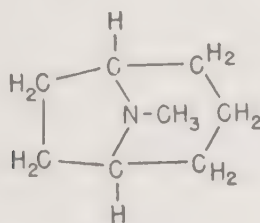
used medicinally, but it is used pharmacologically because of its unique action on the autonomic ganglia, which it first stimulates and then depresses.

Comparison of the toxicities of the synthetic dextrogyrate and the natural levo-gyrate optical isomers indicates that the levo form is twice as toxic as the dextro form. Studies relating to the toxicity of the free base as compared to that of its salts reveals that, whereas nicotine is readily absorbed from the intact skin and the gastro-intestinal tract, the salts are not so easily absorbed.¹¹ First aid measures in nicotine poisoning should be directed toward removal by lavage, if possible, of the toxic material. This should be accompanied by appropriate respiratory support because respiratory failure is the usual cause of death.

TROPANE GROUP

SOLANACEOUS ALKALOIDS

The Solanaceae family furnishes several therapeutically important alkaloids, namely *l*-hyoscyamine, atropine (*dl*-hyoscyamine) and scopolamine (hyoscine). It also yields other alkaloids (e.g., apoatropine, noratropine, belladonnine and meteloidine) which are not used in therapy. The alkaloids may all be considered as being basically derived from *tropane*, a condensed piperidine-pyrrolidine nucleus.



Tropine

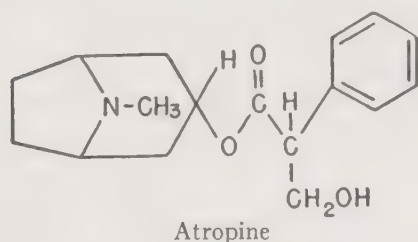
The alkaloids are obtained principally from henbane (*Hyoscyamus niger*), deadly nightshade (*Atropa belladonna*) and Jimson weed (*Datura stramonium*). Officially, the leaves and roots of belladonna are required to contain not less than 0.3 and 0.45 per cent, respectively, of total alkaloids. Stramonium is required to contain at least 0.25 per cent,

and hyoscyamus not less than 0.04 per cent of total alkaloids.

The crude drugs have been used since early times for their marked medicinal properties, which depend largely on a depression of the parasympathetic nervous system and a stimulation of the higher nerve centers. Belladonna, for example, has been used topically for its analgesic effect on hemorrhoids, certain skin infections and various itching dermatoses. The application of sufficient amounts of belladonna or of its alkaloids results in dilatation of the pupil of the eye. Internally, the drug causes diminution of secretions, increases the heart rate (by depression of the vagus nerve), depresses the motility of the gastro-intestinal tract and acts as an antispasmodic on various smooth muscles (ureter, bladder and biliary tract). In addition, it stimulates the respiratory center directly. The very multiplicity of actions exerted by the drug causes it to be looked upon with disfavor, since the physician seeking one type of response unavoidably obtains the others. The action of scopolamine-containing drugs differs from those containing hyoscyamine and atropine in that there is no central nervous system stimulation and a narcotic or sedative effect predominates. The use of this group of drugs is accompanied by a fairly high incidence of reactions due to individual idiosyncrasies, death usually resulting from respiratory failure. The official compendia recognize a variety of products of all three crude drugs, such as tinctures, fluid extracts, extracts, ointments and even a liniment and plaster (e.g., belladonna). A complete treatment of the pharmacology and uses of these drugs is not within the scope of this text, and the reader is referred to the several excellent pharmacologies which are available.

Atropine U.S.P. Atropine is the tropine ester of tropic acid, or more precisely *dl*-tropyl-tropëine. It probably occurs naturally in various *Solanaceae*, although some claim that whatever atropine is isolated from natural sources results from racemization of *l*-hyoscyamine during the isolation process.

It should be pointed out that atropine is optically inactive and that it is the *dl*-racemate of which *l*-hyoscyamine is the levo modification.

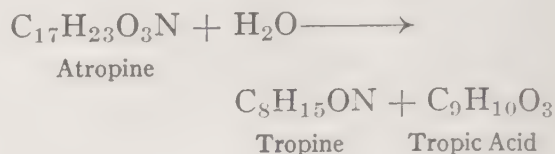


Several methods of isolation are found in the literature, of which the following is more or less typical. The crude drug is powdered, alkalinized with sodium carbonate and fully extracted with ether or ethyl acetate. This extract then is thoroughly extracted with acid (usually acetic). The crude alkaloidal mixture is obtained from the acid solution by alkalinizing it with sodium carbonate and extracting with ether. Appropriate drying and concentration of the ethereal extract yields a crude mixture of atropine and hyoscyamine. To convert the mixture to atropine, the dried residue is mixed with chloroform and refluxed at an elevated temperature for a prescribed period of time. This causes the *l*-hyoscyamine to racemize and form atropine (*dl*-hyoscyamine). The mixture also may be racemized by treating it in the cold with dilute alkali. Because atropine is made by the racemization of hyoscyamine, the U.S.P. sets a limit on the hyoscyamine content by restricting atropine to a maximum levorotation of -0.60° .

Synthetic methods for preparing atropine take advantage of Robinson's synthesis (q.v.), employing modifications to improve the yield of tropinone. The tropinone may be reduced to tropine (tropinol) which is then used to esterify tropic acid. Other acids may also be used in place of tropic acid to form analogues and numerous compounds of this type have been prepared. They are known collectively as tropëines.

The determination of the structure of atropine provides an interesting chapter in

alkaloidal history. It was early recognized that atropine was an ester because of its easy hydrolysis to tropic acid and tropine.



The structure of the tropic acid portion was determined easily, but it was not until Willstätter carried out studies which culminated in its synthesis¹² that the structure of tropine was known with assurance. Compared to Willstätter's somewhat lengthy synthesis (22 steps), that of Robinson,¹³ utilizing acetone, methylamine and succindialdehyde, is indeed simple. (See top of page 427.)

The yields in this synthesis have been improved by using acetone-di-carboxylic acid, its Ca salt or its dimethyl ester in place of acetone.

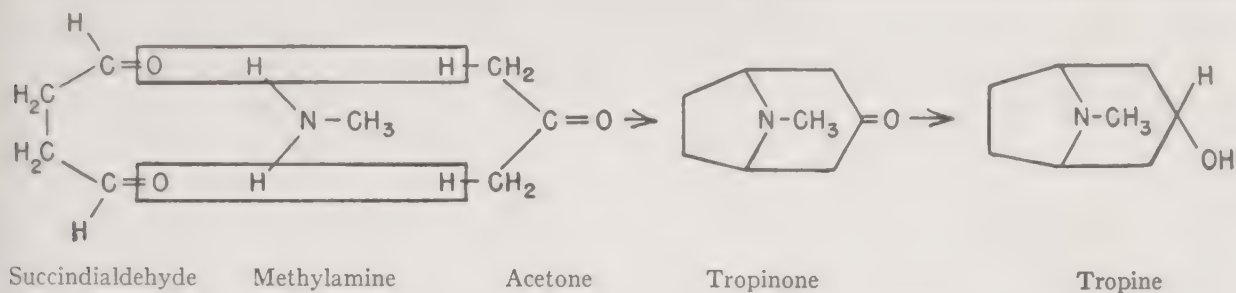
Atropine occurs in the form of optically inactive, white, odorless crystals possessing a bitter taste. It is not very soluble in water (1:460; 1:90 at 80°C .), but is more soluble in alcohol (1:2; 1:1.2 at 60°C .). It is soluble in glycerin (1:27), in chloroform (1:1) and in ether (1:25). Saturated aqueous solutions are alkaline in reaction (approximate $\text{pH}=9.5$). The free base is useful when non-aqueous solutions are to be made, such as in oily vehicles and ointment bases.

The average dose is 0.4 mg.

Atropine Sulfate U.S.P. Atropine sulfate, $(\text{C}_{17}\text{H}_{23}\text{O}_3\text{N})_2 \cdot \text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$, is prepared by neutralizing atropine in acetone or ether solution with an alcoholic solution of sulfuric acid, care being exercised to prevent hydrolysis.

The salt occurs as colorless crystals or as a white crystalline powder. It is efflorescent in dry air and should be protected from light to prevent decomposition.

Atropine sulfate is soluble in water (1:0.5), in alcohol (1:5; 1:2.5 at b.p.) and in glycerin (1:2.5). Aqueous solutions of atropine are not very stable, although it has



been stated¹⁴ that solutions may be sterilized at 120° C. (15 lb. pressure) in an autoclave if the pH is kept below 6. Sterilization probably is best effected by the use of aseptic technic and a bacteriologic filter. The above reference suggests that no more than a 30 day supply of an aqueous solution should be made, and for small quantities, the best procedure is to use hypodermic tablets and sterile distilled water.

The action of atropine or its salts is the same. It produces a mydriatic effect by paralyzing the iris and ciliary muscles, and for this reason, is used by the oculist in *iritis* and *corneal inflammations* and *lesions*. Its use is rational in these conditions because one of the first rules in the treatment of inflammation is rest, which, of course, is accomplished by the paralysis of muscular motion. Its use in the eye (0.5 to 1 per cent solutions or gelatin discs) for *fitting glasses* is widespread. Atropine is administered in small doses *before general anesthesia* to lessen oral and air-passage secretions and, where morphine is administered with it, it serves to lessen the respiratory depression induced by morphine. Its ability to dry secretions is also utilized in the commonly used "rhinitis tablets" for symptomatic relief in *colds*. In *cathartic preparations*, atropine or belladonna acts as an anti-spasmodic to lessen the smooth muscle spasm (gripping) often associated with catharsis. For some purposes it has been found that combinations of the alkaloids of belladonna exert a more desirable action than the single alkaloids. This has been shown, for example, by the acceptance of a mixture of hyoscyamine

hydrobromide, atropine sulfate and scopolamine hydrobromide (Rabellon) or a mixture of alkaloids obtained directly from the Bulgarian belladonna root (*Bellabulgara*) for the treatment of paralysis agitans (Parkinson's disease). This was a consequence of the so-called "Bulgarian Treatment" of this condition in which striking medicinal virtues were claimed for preparations from Bulgarian belladonna root.

The average dose is 0.5 mg.

OFFICIAL OCCURRENCE

N.F.

ATROPINE

Morphine and Atropine Variable, usually

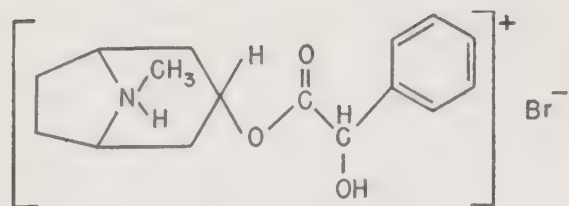
Sulfate Tablets 1/150 grain per tablet

Atropine has been used in numerous other conditions which require depression of the parasympathetic nervous system but, as previously mentioned, it is difficult to elicit one desired reaction without bringing forth other undesirable ones. For this reason, the synthesis of atropine substitutes which possess only one or another of its desirable characteristics has been an active field of investigation. Among the synthetic atropine substitutes which are closely related to atropine are homatropine, homatropine methyl bromide, atropine methyl nitrate and eucatropine.

Homatropine Hydrobromide U.S.P.

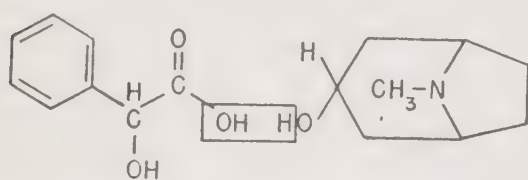
Chemically, this compound is the hydrobromide of mandetyl tropine, and is essentially atropine with the tropic acid residue replaced by mandelic acid.

It may be prepared by evaporating tropine (obtained from tropinone) with mandelic



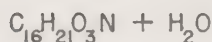
Homatropine Hydrobromide

and hydrochloric acids. The hydrobromide is readily obtained from the free base by neutralization with hydrobromic acid. The hydrochloride (N.N.R., 1947) is obtained in a similar manner.



Mandelic Acid

Tropine



Homatropine

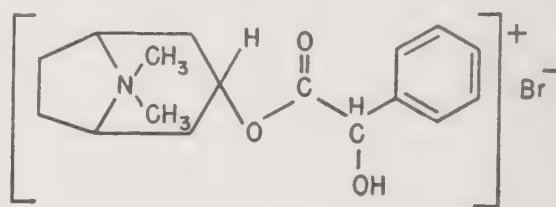
The hydrobromide "occurs as white crystals, or as a white crystalline powder" which is affected by light. It is soluble in water (1:6) and in alcohol (1:40), less soluble in chloroform (1:420) and insoluble in ether.

Solutions are incompatible with alkaline substances, which precipitate the free base, and also with the common alkaloidal reagents. As in the case of atropine, solutions are best sterilized by filtration through a bacteriologic filter, although it is claimed that autoclaving has no deleterious effect.¹⁵

It is used in therapy to paralyze the ciliary structure of the eye (cycloplegia) and to effect mydriasis. It behaves very much like atropine but is weaker. In the eye it acts more rapidly but less persistently than atropine. The dilatation of the pupil takes place in about 15 to 20 minutes, and the action subsides in about 24 hours. By utilizing a miotic such as physostigmine (q.v.), it is

possible to restore the pupil to normality in a few hours. The drug is used in concentrations of 1 to 2 per cent in aqueous solution or in the form of gelatin discs (lamellae).

Homatropine Methylbromide N.F. (Novatropine). This compound is the tropine methyl-bromide ester of mandelic acid. It may be prepared from homatropine by treating it with methyl bromide, thus forming the quaternary compound.



Homatropine Methylbromide

It "occurs as an odorless, white, crystalline powder having a bitter taste. It is affected by light." The compound is readily soluble in water and in alcohol, but is insoluble in ether. Although a solution of the compound yields a precipitate with alkaloidal reagents such as mercuric-potassium-iodide test solution, the addition of alkali hydroxides or carbonates does not cause a precipitate as is the case with nonquaternary nitrogen salts (e.g., atropine, homatropine).

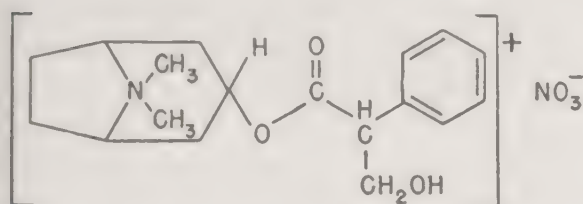
Homatropine methylbromide is said to be less stimulating to the central nervous system than atropine, while retaining a fair measure of its parasympathetic depressant action. It is used orally, in a manner similar to atropine, for lessening oversecretion and to relieve gastro-intestinal spasms.

The average dose is 2.5 mg.

Methyl Atropine Nitrate (Eumydrine, Metanite, Metropine). This compound is a synthetic quaternary derivative of atropine. It is prepared by first making the methyl bromide derivative of atropine, which then is treated with an equivalent amount of silver nitrate.

It occurs in the form of white crystals which are soluble in water. It is precipitated by most of the common alkaloidal reagents

but, being a quaternary ammonium salt, it is not precipitated by alkalis.



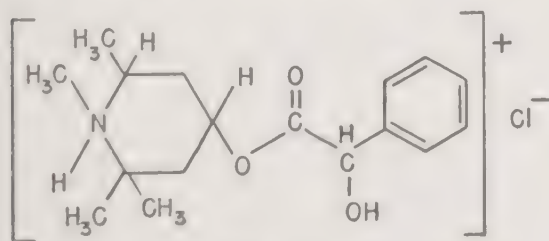
Methyl Atropine Nitrate

It closely resembles atropine in its actions, although it is stated that it is more toxic.¹⁶ When used, it may be given in approximately the same doses as atropine. There seems to be some confusion in the literature as to its toxicity (compared to atropine); Sollmann¹⁷ stated a ratio of 1:50 and Graham and Lazarus¹⁶ a ratio of 3:1.

In the eye, atropine is used in concentrations varying from 1 to 5 per cent for mydriasis and cycloplegia.

Atropine Methylbromide (Mydriazine). This derivative is the methyl bromide addition compound of atropine and is exactly the same type of salt as is found in homatropine methylbromide (q.v.). It occurs as white crystals that are soluble in water or alcohol. Its activity is less than that of atropine, but it is used in 0.5 to 2 per cent concentrations as a mydriatic because of the short recovery period.

Eucatropine Hydrochloride U.S.P. (Euphthalmine Hydrochloride). Eucatropine is the 2,2,6-trimethyl-N-methyl-4-piperidinol ester of mandelic acid. It is very similar to β -eucaine. The hydrochloride is an odorless, white, granular powder that is soluble in water and stable in air.



Eucatropine Hydrochloride

The action of eucatropine closely parallels

that of atropine, but the former is much weaker. It is used as a mydriatic in 5 to 10 per cent solution or in the form of small tablets. Dilatation, with little impairment of accommodation, takes place in about 30 minutes and the eye returns to normal in from 2 to 3 hours.

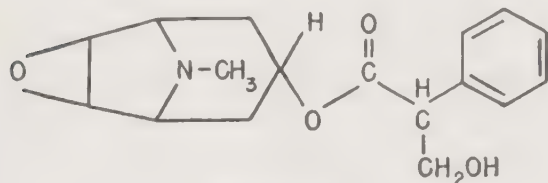
Hyoscyamine. Hyoscyamine is a levorotatory alkaloid obtained from various *Solanaceous* species. One of the commercial sources is Egyptian henbane (*Hyoscyamus muticus*), in which it occurs to the extent of about 0.5 per cent. A recent method for extraction of the alkaloid utilizes *Duboisia* species.¹⁸ Usually it is prepared from the crude drug in a manner similar to that used for atropine and is purified as the oxalate. The free base is easily obtained from this salt.

It occurs as white needles which are sparingly soluble in water (1:281), more soluble in ether (1:69) or benzene (1:150), and very soluble in chloroform (1:1) or alcohol. It was formerly official as the hydrobromide (U.S.P.X). It is also available as the sulfate and the hydrochloride. The principal reason for the popularity of the hydrobromide has been its nondeliquescent nature. The salts have the advantage over the free base in being quite water-soluble.

As mentioned previously, hyoscyamine is the *l*-form of the *dl*-mixture which is known as atropine and, therefore, has the same structure. The *d*-form does not exist naturally, but has been synthesized. Comparison of the activities of *l*-hyoscyamine, *d*-hyoscyamine and *dl*-hyoscyamine (atropine) was carried out by Cushny in 1903. He found that the peripheral action on the iris, cardiac vagus and glands is 12 to 18 times stronger with the *l*-isomer than with the *d*-isomer and twice as strong as with the racemate. All of the isomers behave the same with respect to the central nervous system.

The uses of hyoscyamine are essentially those of atropine, although it is said to be more suited for topical application (i.e., eye) than atropine because its effect is not as prolonged.

Scopolamine (Hyoscine). This alkaloid is found in various members of the *Solanaceae* (e.g., *Hyoscyamus niger*, *Duboisia myoporoides*, *Scopolia* sp. and *Datura metel*).



Scopolamine

It usually is isolated from the mother liquor remaining from the isolation of hyoscyamine.

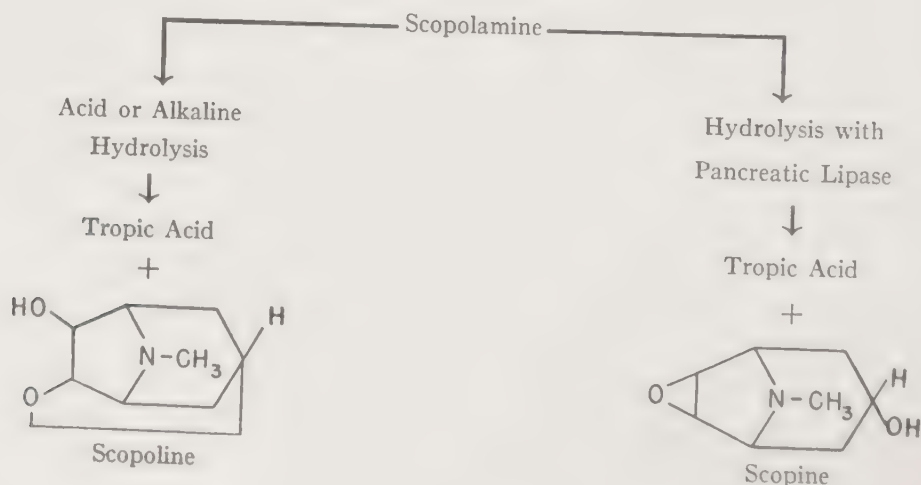
The name *hyoscine* is the older name for this alkaloid, although *scopolamine* is more popular in this country. Scopolamine is the *l*-component of the *dl*-mixture which is known as *atropine*. Scopolamine is readily racemized when subjected to treatment with dilute alkali.

Although scopolamine is very closely related to *l*-hyoscyamine in structure, it was not a simple matter to elucidate the exact structure. Hydrolysis of scopolamine easily yielded *scopoline* (oscine) and tropic acid. However, it soon became evident that scopoline was not the true form in which the basic portion of scopolamine existed in the unhydrolyzed alkaloid, and it was shown that it was a rearranged product. Hydrolysis by less drastic methods, using pancreatic lipase, yielded the true base of scopolamine, namely *scopine*.

The alkaloid occurs in the form of a levorotatory, viscous liquid which is only slightly soluble in water but very soluble in alcohol, chloroform or ether. It forms crystalline salts with most acids, the hydrobromide being the most stable and the most popularly accepted.

Scopolamine Hydrobromide (Hyoscine Hydrobromide) U.S.P. This salt ($C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$) occurs as white or colorless crystals or as a white granular powder. It is odorless and tends to effloresce in dry air. It is soluble in water (1:1.5) or alcohol (1:20), only slightly soluble in chloroform and insoluble in ether.

Scopolamine gives the same type of depression as does atropine on the parasympathetic nervous system, but it differs markedly from atropine in its action on the higher nerve centers. Whereas atropine stimulates the central nervous system, causing restlessness and talkativeness, scopolamine acts as a narcotic or sedative. A sufficiently large dose of scopolamine will cause an individual to sink into a restful, dreamless sleep for a period of some 8 hours, followed by a period of approximately the same length in which the patient is in a semi-conscious state. During this time the patient does not remember events that take place. When scopolamine is administered with morphine, this temporary amnesia is termed "twilight sleep." It has been taken advantage of in obstetric and gynecologic procedures to promote loss of memory about

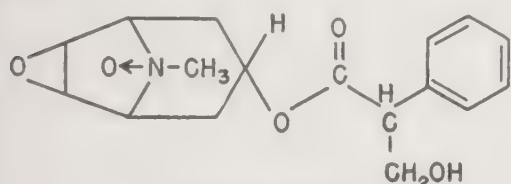


events during labor or during pre-operative or postoperative gynecologic care.

A newer use for scopolamine, largely developed under stress of war, is for motion sickness.¹⁹ While it is not the final answer to the treatment or prevention of travel ills, it is probably one of the best in use today. For prevention, a dose of 0.6 mg. to 0.7 mg. is administered one-half to one hour before the trip commences. The effect lasts for only a few hours.

The average dose is 0.5 mg.

Genoscopolamine. Genoscopolamine is the amine oxide of scopolamine, formed by treating the alkaloid with hydrogen peroxide. It occurs as a white, crystalline powder or in the form of one of its salts (e.g., the hydrobromide).



Genoscopolamine

Because the amine oxide gradually is converted in the body to scopolamine, it exerts the effects of scopolamine, but is said to be much less toxic. It is used for the same purposes as scopolamine. It is given in doses of 1 to 2 mg. daily in divided doses, the dose being gradually increased to 3 or 4 mg. over a period of 6 to 8 days.

COCA AND THE COCA ALKALOIDS

Coca leaves (*Erythroxylon coca*), and a few other related species of coca contain a number of important alkaloids of which *l*-cocaine is the most important from a therapeutic standpoint. For commercial purposes the leaves from South America (Bolivia and Peru) and Java are most used. Among the alkaloids present in the leaves are *l*-cocaine, cinnamyl-cocaine, the truxillines and tropacocaine. These alkaloids, with the exception of tropacocaine, are closely related because acid or alkaline hydrolysis yields *l*-ecgonine and methyl alcohol as common products. The other product of hydrolysis is an acid, which differs in the case of each alkaloid.

Tropacocaine, as noted, does not yield *l*-ecgonine on hydrolysis, but instead gives pseudo-tropine together with benzoic acid. It, therefore, is closely related to atropine. Table 44 (page 432) shows the different constituent portions of the various alkaloids.

Coca leaves have long been used as a stimulant masticatory by the South American Indians to prevent hunger and increase endurance. They are highly habit forming. Because of this, and also due to its toxic nature, the leaf is little used in medicine.

Cocaine U.S.P. Cocaine is defined as "an alkaloid obtained from the leaves of *Erythroxylon coca* Lamarck and other species of *Erythroxylon* (Fam. *Erythroxylaceae*), or by synthesis from ecgonine or its derivatives." Chemically, it is methyl-benzoyl-ecgonine. It occurs to the extent of approximately 1 per cent in South American leaves and to the equivalent (as other derivatives) of about 2 per cent in Java leaves. It was first discovered by Gaedecke (1855), but was rediscovered by Niemann (1859) and named cocaine. Its constitution was elucidated by the combined work of many researchers, among whom Willstätter and his co-workers figured quite prominently.

Since cocaine does not exist naturally to any great extent in any leaves other than those from South America, the usual method of manufacture is not a simple isolation of the active constituent. Commercial methods aim first to isolate the cocaine and related alkaloids from the crude leaves, following which the alkaloids are hydrolyzed either to *l*-ecgonine or, by the use of methyl alcoholic hydrogen chloride, to *l*-ecgonine methyl ester. Following purification of the ecgonine or its derivative by crystallization, *l*-cocaine is synthesized by methylation and benzylation in the case of *l*-ecgonine or by simple benzylation in the case of *l*-ecgonine methyl ester. The reactions at the bottom of page 432 illustrate the manufacture of cocaine.

Cocaine occurs as levorotatory, colorless crystals or as a white, crystalline powder which numbs the lips and tongue when applied topically.

It is slightly soluble in water (1:600; 1:270 at 80° C.), more soluble in alcohol (1:7) and quite soluble in chloroform (1:1) and in ether (1:3.5). The crystals are fairly soluble in olive oil (1:12), but less soluble in mineral oil (1:80 or 100). Because of its solubility characteristics, it is used principally where oily solutions or ointments are indicated.

Cocaine is basic and readily forms crystalline salts such as the benzoate, borate, citrate, hydrochloride, hydrobromide, hydriodide and salicylate. The hydrochloride is official in the U.S.P. Ordinarily, the salt form is useful only from the standpoint of its solubility in water, but among the cocaine salts there seems to be some evidence to indicate that a superior anesthetic action may be obtained from the salicylate (4 times as active as hydrochloride).²⁰ From a stability standpoint, solutions of cocaine borate are claimed to be more stable than those of the hydrochloride.

Cocaine Hydrochloride (Cocaini Hydrochloridum P. I.) U.S.P. This cocaine salt ($C_{17}H_{21}O_4N \cdot HCl$) occurs "as colorless crystals, or as a white, crystalline powder." The salt is soluble in water (1:0.5), alcohol (1:3.5), chloroform (1:15) or glycerin. It is insoluble in ether.

Solutions are incompatible with calomel, mercuric oxide, silver nitrate, sodium borate, triethanolamine, alkalies and the usual alkaloidal precipitants. Sterilization of aqueous solutions cannot be effected by boiling because of decomposition to benzoyl *l*-ecgonine and methanol. The best method of sterilization probably is by filtration through a bacteriologic filter.

Although solutions of cocaine hydrochloride are fairly stable, it is sometimes necessary that the solution be as near to neutrality as possible. In this case, attainment of a pH of 7 to 7.2 by using a buffered solution (e.g., phosphate buffer, pH=7.2) will prevent precipitation, although the solution then becomes considerably less stable.

The local anesthetic properties of cocaine were first demonstrated by Wohler in 1860.

Koller, however, first used the drug in 1884 as a topical anesthetic in the eye. Its toxicity has prevented cocaine from being used for anything other than topical anesthesia and, even in this capacity, it is desirable to limit its use for fear of causing systemic reactions and addiction. It is easily absorbed from mucous membranes, as is evidenced by the quick response obtained by addicts when cocaine ("snow") is snuffed into the nostrils. It is worthy of note that cocaine does not penetrate through the intact skin. As a local anesthetic it is used in the *eye* in concentrations up to 4 per cent. The anesthesia produced by such concentrations lasts approximately one-half an hour. Its use in ophthalmology is marred by the fact that not infrequently it causes corneal damage with resultant opacity. For *nose* and *throat* work, concentrations higher than 10 per cent are rarely used, 4 per cent being a common concentration. In any case, the total amount of cocaine used should not exceed 0.1 Gm. More detailed summaries of its uses may be consulted in the literature.²¹

The sterilization difficulties, coupled with the habit-forming tendencies of cocaine, have resulted in a great deal of research aimed toward the production of more desirable local anesthetics. Since the discovery of procaine (novocaine) by Einhorn in 1905 (q.v.), a host of compounds possessing local anesthetic properties have been synthesized.

Tropacocaine. This alkaloid occurs in Javanese coca or it may be prepared synthetically by the esterification of benzoic acid with pseudotropine. The latter is the commercial procedure.

It is marketed as the hydrochloride, which occurs as colorless needles, slightly soluble in alcohol, but readily soluble in water to form a neutral solution.

The compound, although more irritant than cocaine, is reported to have approximately the same anesthetic action with one-half the toxicity. Furthermore, it is more stable. It is used principally in spinal anesthesia.

LUPINANE GROUP

Henry prefers to call the members of this group "the alkaloids of the *Papilionaceae*" rather than the usual "lupin alkaloids." In spite of their occurrence in the lupines, he feels that their extensive distribution throughout this particular leguminous subfamily warrants the new terminology. The lupines themselves are of great economic importance because of the poisonous nature of some members of the genus toward feeding livestock. In some sections of the West certain species of lupines are known as "loco weed" in allusion to the behavior of animals that have eaten the plants. The toxicity is directly attributable to the alkaloidal content of the plants, and much attention has been directed toward removal of these alkaloids to render the plants suitable for feeding purposes. Among the alkaloids which are present in lupines are lupinine, sparteine, cytisine, monolupine, dilupine, trilupine, etc. Sparteine is the only one of these alkaloids that has been used medicinally.

Sparteine Sulfate N.F. Broom, the dried tops of *Cytisus scoparius*, was formerly official in N.F.V. It was used as a diuretic and one of its principal components was the alkaloid, sparteine. Sparteine may be prepared by extraction procedures from dried and ground broom tops or it may be prepared synthetically.²² The free base occurs as a levorotatory oil. It possesses two basic nitrogens and is easily converted into its salts. The most important salt is the sulfate, $C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$, which occurs "as colorless, rhombohedral crystals, or as a white, crystalline powder." The salt is odorless, has a somewhat bitter taste and is slightly hygroscopic.

The sulfate is quite soluble in water (1:1.1) and in alcohol (1:3), but is insoluble in chloroform or ether. Aqueous solutions are neutral or slightly acid to litmus and may be autoclaved. Solutions possess the usual alkaloidal incompatibilities.

Medicinally, sparteine is apparently of little value, although at one time it was held

in esteem as a substitute for digitalis in cardiac arrhythmias. This was because of its definitely depressant effect on the heart. Sparteine has been used since early days for the treatment of dropsy, but this use has been proven to be without firm basis. As a diuretic, sparteine largely has been superseded by other, more effective drugs. Recently,²³ the drug has been suggested as an oxytocic based on a uterine stimulating action.

The average dose is 30 mg.

ISOQUINOLINE GROUP

CACTUS AND ITS ALKALOIDS

The flowering heads of *Anhalonium Lewinii*, known as "mescal buttons," first came to the attention of investigators because of their use in certain religious ceremonies by natives of Mexico and the southwestern United States. For an account of their use in this capacity, the reader is referred to the interesting accounts by Lewin,²⁴ Beringer²⁵ and Castetter and Opler.²⁶ The most interesting effect of this plant is the production of beautiful color and sound hallucinations. These, however, are accompanied by physical effects such as nausea, faintness, muscular relaxation, headache and associated ill effects. The effects of mescal buttons are due to the presence of numerous alkaloids, among which are mescaline, anhalamine, anhalidine, anhalinine, anhalonidine, anhalonine, lophophorine and pellotine. Of these, mescaline is probably the alkaloid to which most of the hallucinating properties may be attributed. Although mescaline itself is not an isoquinoline type alkaloid, it is considered here because it is very likely a precursor to the other alkaloids which are of the isoquinoline type.

Mescaline. This alkaloid, $C_{11}H_{17}O_3N$, may be isolated from the natural source or, more commonly, it may be synthesized by the conventional syntheses for β -phenylethylamine compounds (q.v.).

The free base occurs as white crystals or as an oil which is moderately soluble in water, alcohol or chloroform, but insoluble

in ether. Mescaline readily absorbs atmospheric carbon dioxide to form a crystalline carbonate. The base contains one basic nitrogen and, thus, forms salts readily. The sulfate, $(C_{11}H_{17}O_3N)_2 \cdot H_2SO_4 \cdot 2H_2O$, occurs as white crystals which are only sparingly soluble in cold water but freely soluble in hot water.

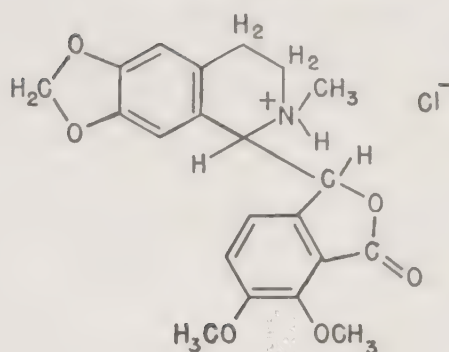
Although mescaline is not used medicinally, it has been receiving attention as a possible tool for the study of schizophrenics. It is believed by some investigators that the ability of mescaline to produce experimental hallucinations may be the key to an understanding of the incompletely understood hallucinatory condition in schizophrenia.

HYDRASTIS AND HYDRASTIS ALKALOIDS

The dried rhizome and roots of goldenseal (*Hydrastis canadensis*) constitute the official "Hydrastis" of the N.F. The drug contains three alkaloids, namely, hydrastine, berberine and canadine. Hydrastis is officially required to contain at least 2.5 per cent of the ether-soluble alkaloids calculated on an anhydrous basis. Of the alkaloids present, the only one of any medicinal importance is hydrastine.

Hydrastis itself, or in the form of any of its galenical preparations, is said to exert a hemostatic action on the uterus by stimulating the musculature and consequently compressing the blood vessels. It is infrequently used also as an oxytocic and emmenagogue because of the uterine contractions induced.

Hydrastine Hydrochloride N.F. This base was first recognized by Durand in 1851, but our knowledge of its structure is principally due to the work of E. Schmidt and M. Freund. It is very closely related to narcotine. The free base, hydrastine, is obtained from the crude plant by the usual isolation procedures and is purified through the bitartrate. It occurs as levorotatory white prisms or as a crystalline powder which is water-insoluble



Hydrastine Hydrochloride

It contains basic nitrogen and is easily converted to various salts, of which the hydrochloride is used medicinally. The hydrochloride, $C_{21}H_{21}O_6N \cdot HCl$, occurs as a white to creamy-white, odorless, hygroscopic powder which is very soluble in water or alcohol, but much less soluble in ether or chloroform. Aqueous solutions are acid to litmus and may be sterilized by the application of heat.

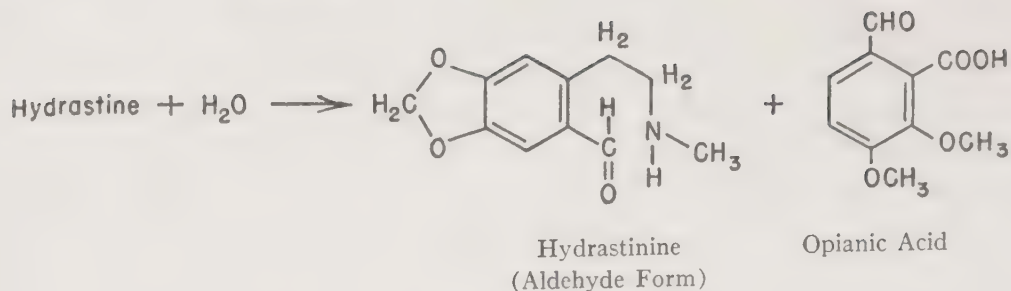
This salt has been used for the same purpose as crude hydrastis, namely as a uterine stypic when administered internally. It is doubtful whether the salt is of justifiable value in this capacity. When applied externally, it exerts an astringent action on mucous membrane. It may, therefore, be used for ophthalmic instillation to reduce the inflammation incident to conjunctivitis and to reduce capillary bleeding. Solutions of 0.1 to 0.5 per cent commonly are used externally. The occurrence of the salt in commercial astringent preparations is based on the hemostatic effect of hydrastine.

The average dose is 10 mg.

Hydrastinine. When hydrastine is subjected to acid oxidation, it undergoes oxidative hydrolysis to yield hydrastinine and opianic acid. The reaction is entirely analogous to that of narcotine, which yields cotarnine and opianic acid (q.v.).

The formula of hydrastinine is very similar to that of cotarnine except that it lacks a methoxyl group.

Although it is probable that hydrastinine does not exist in the closed ring form as the free base, it is believed that, upon treat-



ment with an acid (e.g., hydrochloric acid), ring formation takes place (see cotarnine). As with cotarnine, the salt which forms is quaternary in nature and is more properly termed a "chloride" than a "hydrochloride."

It is used infrequently for the same purposes as is hydrastine, and is said by some to be preferable to hydrastine because it has less action on the central nervous system (stimulant) and heart (depressant). Its usefulness as a uterine hemostatic does not extend to postpartum hemorrhage. It is administered in a dose of approximately 30 mg.

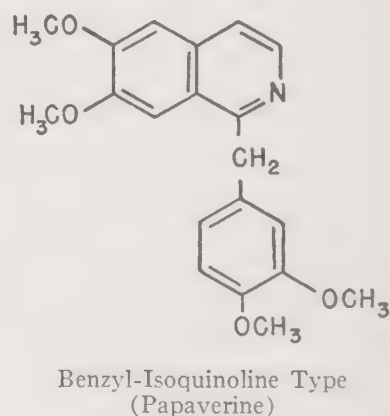
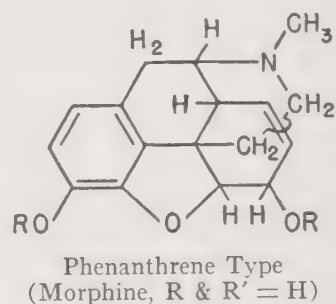
PAPAVERACEOUS ALKALOIDS

Opium is the partly dried latex from incised unripe capsules of *Papaver somniferum*. It contains numerous alkaloids (as meconates and sulfates), of which morphine, codeine and papaverine are therapeutically the most important. Other alkaloids, such as narceine and narcotine, also have been tested medicinally, but are not of great importance. The action of opium is due principally to its morphine content. As an analgesic, opium is not as effective as morphine because of its slower absorption, but it has a greater constipating action and is thus better suited for antidiarrheal preparations (e.g., paregoric). Opium, as a constituent of Dover's powders and Brown Mixture, also exerts a valuable expectorant action which is superior to that of morphine.

Two types of basic structures usually are recognized among the opium alkaloids, i.e., the *phenanthrene* (morphine) type and the *benzyl-isoquinoline* (papaverine) type.

The pharmacologic actions of the two types of alkaloids are dissimilar. The mor-

phine group acts principally on the central nervous system as a depressant and stimulant, whereas the papaverine group has little effect on the nervous system but has a marked antispasmodic action on smooth muscle.



Clinically, the depressant action of the morphine group is the most useful property, resulting in a raising of the pain threshold, a sleepy feeling, a lessened perception to external stimuli and a feeling of well-being (euphoria). Respiratory depression, central in origin, is perhaps the most serious objection to this type of alkaloid, aside from its tendency to cause addiction. The stimulant action is well illustrated by the convulsions produced by certain members of this group

(e.g., thebaine). Consideration of the morphine formula shows two OH groups, one alcoholic and the other phenolic. Alteration of the alcoholic group by acetylation, oxidation or entire removal increases the central depressant action, whereas alkylation of the phenolic group (e.g., codeine) tends to elicit the central stimulant properties.

As previously stated, one of the drawbacks to the general use of these drugs is the possibility of addiction, even with the use of therapeutic doses. Intensive effort has been directed toward improvement of the analgesic action and elimination of the habit-forming tendencies. In spite of all this work, only three of the recent synthetic drugs have offered qualities at all comparable to morphine. They are Meperidine (Demerol), Metopon and Methadon. Unfortunately, complete elimination of the addictive tendencies of morphine has not been effected even with these compounds. Meperidine and Methadon are discussed elsewhere in this text but, Metopon as being closely related structurally to morphine, will be considered in this chapter. Aside from these newer drugs, there are some older synthetic derivatives of morphine. The structural similarities will become apparent by an inspection of Table 45 (page 438).

The papaverine type of alkaloid, as stated, is primarily a smooth muscle depressant. Because it acts directly on the muscle cell, it is said to be a *musculotropic* antispasmodic, in contrast to other drugs (e.g., atropine), which act on the nerves and, consequently, are of the *neurotropic* type. The most pronounced action exerted by this group is on the smooth muscle of the blood vessels. Because papaverine is the only member of this group, a further discussion of its effects will be deferred until papaverine itself is discussed.

Morphine Type (Natural and Synthetic)

Morphine. This alkaloid was first isolated in 1803 by Derosne, but the credit for isolation generally goes to Serturmer (1805) who

first called attention to the basic properties of the substance. Morphine, incidentally, was the first plant base isolated and recognized as such. Although intensive research was carried out with respect to the structure of morphine, it was only in 1925 that Gulland and Robinson²⁷ postulated the currently accepted formula. The total synthesis of morphine has not yet been effected.

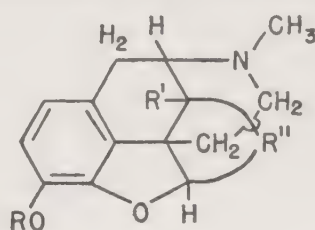
Morphine is obtained only from opium, in which it occurs in amounts varying from 5 to 20 per cent (U.S.P. requires 10 to 10.5 per cent). It is isolated by various methods of which the final step is usually the precipitation of morphine from an acid solution by using excess ammonia. The precipitated morphine is then recrystallized from boiling alcohol.

The free alkaloid, $C_{17}H_{19}O_3N \cdot H_2O$, occurs as levorotatory, odorless, white, needle-like crystals possessing a bitter taste. It is almost insoluble in water (1:5,000, 1:1,100 at b.p.), ether (1:6,250) or chloroform (1:1,220). It is somewhat more soluble in ethyl alcohol (1:210, 1:98 at b.p.) and in methyl alcohol (1:10 at b.p.). Because of the phenolic hydroxyl group, it is readily soluble in solutions of alkali or alkaline earth metal hydroxides.

Morphine is a mono-acidic base and readily forms water-soluble salts with most acids. Thus, because morphine itself is so poorly soluble in water, the salts are the preferred form for most uses. Numerous salts have been marketed, but the ones in use are principally the sulfate and, to a lesser extent, the hydrochloride.

Many writers have pointed out the "indispensable" nature of morphine, based on its potent analgesic properties toward all types of pain. However, because it causes addiction so readily, it should be used only in those cases where other pain-relieving drugs prove inadequate. It controls pain caused by serious injury, carcinoma, migraine, pleurisy, biliary and renal colic, and numerous other causes. It is often administered as a pre-operative sedative together

TABLE 45. SYNTHETIC DERIVATIVES OF MORPHINE



COMPOUND	R	R'	R''	PRINCIPAL USE
Morphine	H	H		Analgesic
Codeine	CH ₃	H	same as above	Depress cough reflex
Ethylmorphine (Dionin)	C ₂ H ₅	H	same as above	Ophthalmology
Diacetyl morphine (Heroin)	CH ₃ CO	H		Analgesic (prohibited in U.S.)
Dihydromorphinone (Dilaudid)	H	H		Analgesic
Dihydrocodeinone (Dicodid)	CH ₃	H	same as above	Analgesic and to depress cough reflex
Dihydro-hydroxy- codeinone (Eukodal)	CH ₃	OH	same as above	Analgesic and to depress cough reflex
Dihydrocodeine (Paracodin)	CH ₃	H		Depress cough reflex
Dihydromorphine	H	H	same as above	Analgesic
Dihydro-desoxy- morphine-D (Desomorphine)	H	H		Analgesic
Dihydro-desoxy- codeine-D (Desocodeine)	CH ₃	H	same as above	Analgesic
Methyl dihydro- morphinone (Metopon)	H	H		Analgesic

with atropine to control secretions. With scopolamine, it is given to obtain the so-called "twilight sleep." This effect is used in obstetrics, but care is exercised to prevent respiratory depression in the fetus. It is worthy of note that the toxic properties of morphine are much more evident in the very young and very old than in middle-aged people.

Morphine Hydrochloride N. F. This salt, $C_{17}H_{19}O_3N.HCl.3H_2O$, may be prepared by neutralizing a hot aqueous suspension of morphine with diluted hydrochloric acid and then concentrating the resultant solution to crystallization.

It occurs "as white, silky, glistening needles or cubical masses, or as a white crystalline powder." The hydrochloride is soluble in water (1:17.5, 1:0.5 at b.p.), alcohol (1:52, 1:46 at 60° C.) or glycerin, but it is practically insoluble in ether or chloroform. Solutions have an approximate pH of 4.7 and may be sterilized by boiling.

Its uses are the same as those of morphine.

The average dose is 8 mg.

Morphine Sulfate U.S.P. This morphine salt, $(C_{17}H_{19}O_3N)_2.H_2SO_4.5H_2O$, is prepared in the same manner as the hydrochloride, i.e., neutralizing morphine with diluted sulfuric acid.

It occurs "as white, feathery, silky crystals, as cubical masses of crystals, or as a white, crystalline powder." While it is a fairly stable salt, it loses water of hydration and darkens on exposure to air and light. It is soluble in water (1:16, 1:1 at 80° C.), poorly soluble in alcohol (1:570, 1:240 at 60° C.) and insoluble in chloroform or ether. Aqueous solutions have a pH of approximately 4.8 and may be sterilized by heating in an autoclave.

It has the uses of morphine.

The average dose is 10 mg.

OFFICIAL OCCURRENCE

N.F.

Morphine and Atropine Sulfates Tablets

MORPHINE

Variable, tablets may commonly contain 8, 10, 15 or 30 mg.

Codeine N.F. Codeine, $C_{18}H_{21}O_3N.H_2O$, is an alkaloid which occurs naturally in opium, but the amount present is usually too small to be of commercial importance. Consequently, most commercial codeine is prepared from morphine by methylating the phenolic hydroxyl group. The methylation methods are usually patented procedures and make use of such reagents as diazomethane, dimethyl sulfate and methyl iodide.

It occurs as levorotatory, colorless, efflorescent crystals or as a white, crystalline powder. It is light-sensitive. Codeine is somewhat soluble in water (1:120) and in ether (1:50), but it is readily soluble in alcohol (1:2) and in chloroform (1:0.5).

Codeine is a mono-acidic base and readily forms salts with acids; the most important salts are the sulfate and the phosphate. The free base is used little as compared to the salts, its greatest use being in Terpin Hydrate and Codeine Elixir.

The general pharmacologic action of codeine is similar to that of morphine but, as previously indicated, it does not possess to the same degree the potent analgesic properties of the latter. However, it is used extensively for its analgesic action in combination with such drugs as acetylsalicylic acid and phenacetin. It has a lesser sedative effect on the respiratory center than morphine, but is effective in depressing the cough reflex. To this end it is probably one of the most widely incorporated ingredients of cough preparations in use today. It is particularly valuable because there seems to be little tendency toward addiction and negligible respiratory depression in the usual doses. A combination of codeine and papaverine (Copavin) has been advocated by Diehl²⁸ for prophylaxis and treatment of common colds. If administered at the first signs of a cold, it is claimed to abort the cold in a significant percentage of the cases.

The average dose is 30 mg.

OFFICIAL OCCURRENCE

N.F.

Terpin Hydrate and Codeine Elixir

PER CENT CODEINE

0.2

Codeine Phosphate U.S.P. This salt, $C_{18}H_{21}O_3N \cdot H_3PO_4 \cdot 1\frac{1}{2}H_2O$, may be prepared by neutralizing codeine with phosphoric acid and precipitating the salt from aqueous solution with the aid of alcohol.

Codeine phosphate "occurs as fine, white, needle-shaped crystals or as a white, crystalline powder." It is efflorescent and is sensitive to light. It is very soluble in water (1:2.5, 1:0.5 at 80° C.) but less soluble in alcohol (1:325; 1:125 at b.p.). Solutions may be sterilized by boiling.

Because of its high solubility in water as compared to the sulfate, this salt is widely used. It is often the only salt of codeine stocked by pharmacies and is dispensed, rightly or wrongly, on all prescriptions calling for either the sulfate or phosphate.

It has the same uses as codeine.

The average dose is 30 mg.

OFFICIAL OCCURRENCE	PER CENT CODEINE PHOSPHATE
N.F.	
Compound White Pine Syrup with Codeine	0.2

Codeine Sulfate U.S.P. Codeine sulfate, $(C_{18}H_{21}O_3N)_2 \cdot H_2SO_4 \cdot 5H_2O$, is prepared by neutralizing an aqueous solution of codeine with diluted sulfuric acid and then effecting crystallization.

It occurs "as white crystals, usually needle-like, or as a white, crystalline powder." The salt is efflorescent and light-sensitive. It is soluble in water (1:30, 1:6.5 at 80° C.), much less soluble in alcohol (1:1,280) and insoluble in ether or chloroform.

This salt of codeine is prescribed frequently, but is not as suitable as the phosphate for liquid preparations. Solutions of the sulfate and phosphate are incompatible with alkaloidal reagents and alkaline substances.

Codeine sulfate is used for the same purposes as codeine.

The average dose is 30 mg.

Ethylmorphine Hydrochloride U.S.P. (Dionin). This synthetic compound,



is analogous to codeine, but instead of being the methyl ether it is the ethyl ether. Ethylmorphine may be prepared by treating an alkaline alcoholic solution of morphine with diethyl sulfate. The hydrochloride is obtained from the free base by neutralizing it with diluted hydrochloric acid.

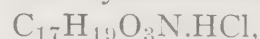
The salt "occurs as a white, or faintly yellow, odorless, microcrystalline powder." It has a slightly bitter taste. It is soluble in water (1:10) and in alcohol (1:25) but only slightly soluble in ether and in chloroform.

The systemic action of this morphine derivative is intermediate between that of codeine and morphine. It has analgesic qualities and sometimes is used for the relief of pain. As a depressant of the cough reflex, it is as effective as codeine and, for this reason, is found in some commercial cough syrups. However, the chief use of this compound is in ophthalmology. By an irritant dilating action on vessels it stimulates the vascular and lymphatic circulation of the eye.

The average dose is 15 mg.

Dihydromorphinone Hydrochloride U.S.P. (Dilaudid). Dilaudid is a synthetic derivative of morphine. It is prepared by the reduction and oxidation of morphine.

The free base has basic properties similar to those of morphine and readily forms a hydrochloride. The hydrochloride,



occurs as a light-sensitive, white, crystalline powder which is soluble in water (1:3), sparingly soluble in alcohol and nearly insoluble in ether.

This compound is of German origin and was introduced in 1926. It is a substitute for morphine (5 times as potent) but has approximately equal addicting properties and a lesser duration of action. However, it is said that addiction takes place more slowly than with morphine. Because its narcotic effect is not as great in proportion to its analgesic effect, it possesses the advantage over morphine of causing less daytime

drowsiness. It has a powerful effect upon the cough reflex and occasionally is incorporated into cough syrups for difficultly controllable coughs. It is used in about one-fifth the dose of morphine for any of the indications of morphine.

The average dose is 2 mg.

Methyldihydromorphinone (Metopon).

This morphine derivative is one of the newest to be announced.²⁹ It has been estimated that the analgesic action of this new derivative is substantially more than that of morphine with no more toxicity or addiction liability. Indeed, investigators have found that placement of confirmed morphine addicts on a Metopon regime failed to adequately control the morphine withdrawal symptoms. Taking the lack of control of withdrawal symptoms as an indication of its addictive potentialities, it would appear that Metopon is, therefore, less liable to produce addiction than morphine. The drug is very effective orally and, because it elicits practically no emetic action, it is suitable for prolonged administration. It is marketed only for oral consumption in the form of 3 mg. capsules. The dose of the hydrochloride is from 6 to 9 mg., and the dose is to be repeated only on the recurrence of pain. Around-the-clock medication is to be avoided because it is conducive to habituation. The drug is primarily suggested for the relief of pain in the treatment of such conditions as inoperable cancer. A narcotic form is required to obtain the drug.

Dihydrocodeinone (Dicodid, Mercodione). This compound bears a close resemblance to dilaudid. It is stated to have a physiological action midway between that of codeine and morphine, with 15 mg. being equivalent to 10 mg. of morphine in analgesic power. It is of use in allaying coughs and as an analgesic for relief of pain. It is used in the form of the hydrochloride or the bitartrate in a dose of 15 mg. subcutaneously. Both of the salts are freely soluble in water.

Dihydrohydroxycodeinone Hydrochloride (Eukodal, Eucodal). This derivative of

morphine occurs as a white crystalline powder which is soluble in water (1:10) or alcohol. Aqueous solutions may be sterilized by boiling.

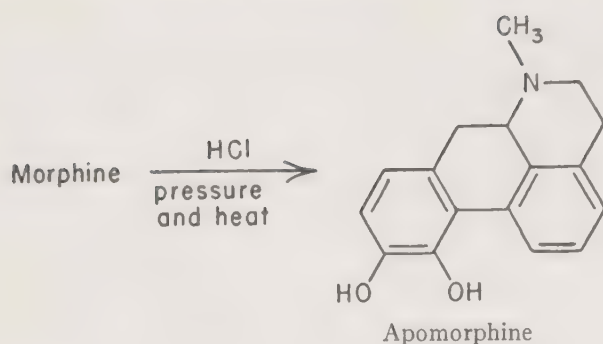
It is used as a sedative, analgesic and narcotic. Because it is believed to exert a physostigminelike action, it is used externally in the eye in the treatment of glaucoma and related ocular conditions. To depress the cough reflex it is used in 3 to 5 mg. doses and as an analgesic in 5 to 10 mg. doses. For severe pain a dose of 20 mg. is given subcutaneously.

Dihydrocodeine Bitartrate (Paracodin Tartrate). This salt occurs in the form of white crystals which are soluble in water (1:4.5) but only slightly soluble in alcohol. It is useful for the same purposes as codeine, namely to control the cough reflex. The dose is from 10 to 50 mg.

Pantopon. Pantopon consists of a mixture of the total alkaloids of opium. It is free of nonalkaloidal material, and the alkaloids are said to be present in the same proportions as they occur naturally. The alkaloids are in the form of the hydrochlorides, and morphine constitutes 50 per cent of the weight of the material.

This preparation is promoted as a substitute for morphine, the claim being that it is superior to the latter due to the synergistic action of the opium alkaloids. This synergism is said to result in less respiratory depression, less nausea and vomiting and an antispasmodic action on smooth muscle. According to Goodman and Gilman, however, the superiority to morphine is overrated and the effects produced are comparable to the use of an equivalent amount of morphine. The commercial literature suggests a dose of 1/3 grain of pantopon to obtain the same effect as is given by 1/4 grain of morphine.

Apomorphine Hydrochloride U.S.P. When morphine or morphine hydrochloride is heated at 140° C. under pressure with strong (35 per cent) hydrochloric acid, it loses a molecule of water and yields a compound known as apomorphine.



Inspection of the resultant formula shows a rupture of the ether bridge of morphine, a rearrangement of the point of attachment of the ethanamine chain and the formation of a benzene ring. Apomorphine is soluble in ether or chloroform, whereas morphine is not. Separation of the former from unreacted morphine is effected by precipitating both phenolic bases with excess sodium bicarbonate and then selectively extracting the apomorphine from the mixture with ether or chloroform. The hydrochloride may be obtained by neutralizing the free base with diluted hydrochloric acid and crystallizing.

The hydrochloride,



is odorless and occurs "as minute, white or grayish white, glistening crystals or white powder." It is light-sensitive and turns green on exposure to air and light. It is soluble in water (1:50, 1:20 at 80° C.) and in alcohol (1:50), but is practically insoluble in ether or chloroform. Solutions are neutral to litmus.

The change in structure from morphine to apomorphine causes a profound change in its physiologic action. The central depressant effects of morphine are much less pronounced and the stimulant effects are greatly enhanced. In particular, the vomiting center is stimulated and the emesis produced by apomorphine, therefore, is purely central in origin. It is administered subcutaneously to obtain emesis. It is ineffective orally. Apomorphine is one of the most effective, prompt (10 to 15 minutes) and safe emetics in use today. However, care should be exercised

in its use since it may be depressant in already depressed conditions.

The average dose is 5 mg. subcutaneously.

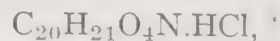
Benzyl Isoquinoline Type

Papaverine and narcotine are the only important naturally occurring members of this group. Synthetic derivatives of papaverine have been made in an effort to enhance the antispasmodic effects. These are discussed elsewhere in this text (see, for example, Sestron).

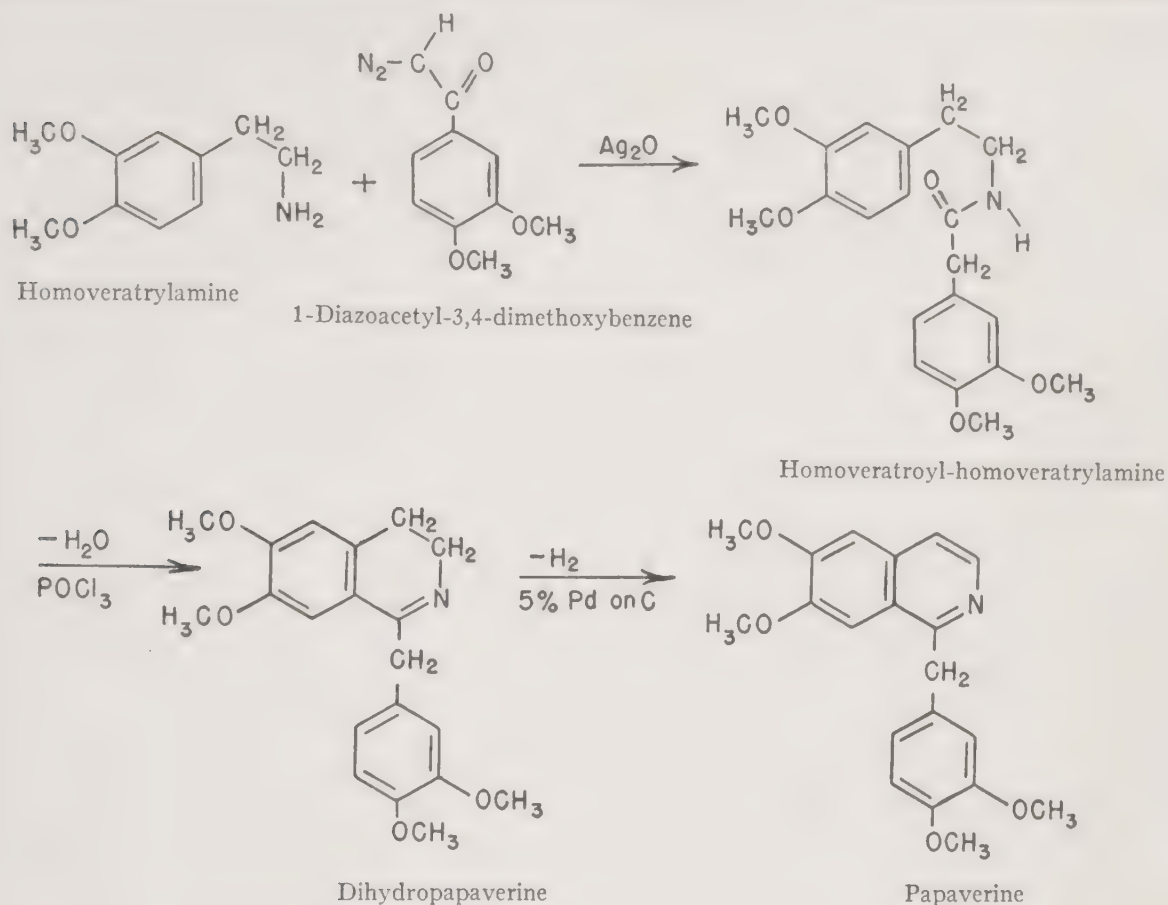
Papaverine Hydrochloride U.S.P. This alkaloid was first isolated by Merck (1848) from opium, in which it occurs to the extent of about 1 per cent. Its structure was elucidated by the classical researches of Goldschmiedt, and its synthesis was first effected by Pictet and Gams in 1909.

Previous to the last war, papaverine had been obtained in sufficient quantities from natural sources. However, as a result of the war, the United States found itself early in 1942 without a source of opium and, therefore, of papaverine. Consequently, the commercial synthesis of papaverine took on a new significance and methods were soon developed to synthesize the alkaloid on a large scale. The synthesis shown at the top of page 443 is of interest because it shows an ingenious application of the Arndt-Eistert step-up in the initial reaction.³⁰

Papaverine itself, $\text{C}_{20}\text{H}_{21}\text{O}_4\text{N}$, occurs as an optically inactive, white crystalline powder. It possesses one basic nitrogen and forms salts quite readily. The most important salt is the hydrochloride,



which is official. The hydrochloride "occurs as white crystals or as a white, crystalline powder." It is not optically active, is odorless and has a slightly bitter taste. The compound is soluble in water (1:30), alcohol or chloroform. It is not soluble in ether. Aqueous solutions are acid to litmus and may be sterilized by autoclaving. Unless properly handled and stored, extemporaneous



solutions of papaverine salts deteriorate rapidly.

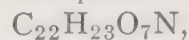
Because of the antispasmodic action of papaverine on blood vessels, it has become extremely valuable for relieving the arterial spasm associated with acute vascular occlusion. It is useful in the treatment of peripheral, coronary and pulmonary arterial occlusions. Administration of an antispasmodic is predicated on the concept that the lodgement of an embolus causes an intense reflex vasospasm. This vasospasm affects not only the artery involved, but the surrounding blood vessels as well. Relief of this neighboring vasospasm is imperative in order to prevent damage to these vessels and to limit the area of ischemia. Therefore, it appears to act by increasing collateral circulation in the affected area rather than by acting on the occluded vessel.

Other than its antispasmodic action on the vascular system, it is used for bronchial

spasm and visceral spasm. In the latter type of spasm it is not advisable to administer morphine simultaneously because it opposes the relaxing action of papaverine.

The average dose is 0.1 Gm. orally or intravenously.

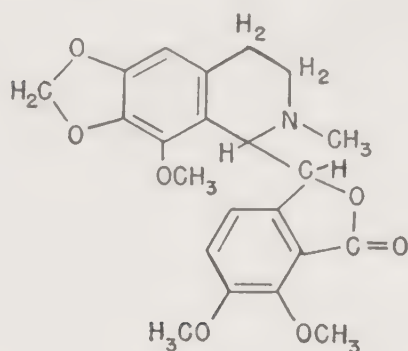
Narcotine. This opium alkaloid,



was isolated in 1817 by Robiquet. It is rather easily isolated from the drug by ether extraction. It exists to the extent of 0.75 to 9 per cent in opium. The present knowledge of its structure is largely due to the researches of Roser.

Narcotine base occurs as levorotatory, colorless prisms. It is difficultly soluble in water but is more soluble in the immiscible solvents, particularly chloroform. It is not soluble in cold alkali but is readily soluble in hot alkali, due to the opening of the lactone ring with consequent salt formation. It possesses a basic nitrogen and, for this rea-

son, forms water-soluble salts such as the hydrochloride.



Narcotine

Although narcotine has been used therapeutically as an antispasmodic (similar to papaverine), antineuralgic and antiperiodic, it is little used today. Perhaps its chief importance lies in its being the source of the officially recognized cotarnine chloride.

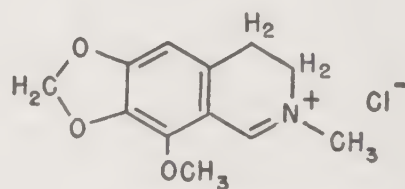
Cotarnine Chloride (Cotarnine Hydrochloride) N. F. (Stypticin).

As previously indicated, cotarnine is manufactured from narcotine. Narcotine is subjected to an oxidative hydrolysis, using nitric acid as the oxidizing agent. The products are cotarnine and opianic acid.

Cotarnine chloride may be made by dissolving cotarnine in hydrochloric acid and evaporating the resulting solution to dryness. Evidence points to the fact that the salt forms from the quaternary base form (see above) of cotarnine rather than from any of the other possibilities. This being the case, the salt is a "chloride" and not a "hydrochloride."

Quaternary Cotarnine

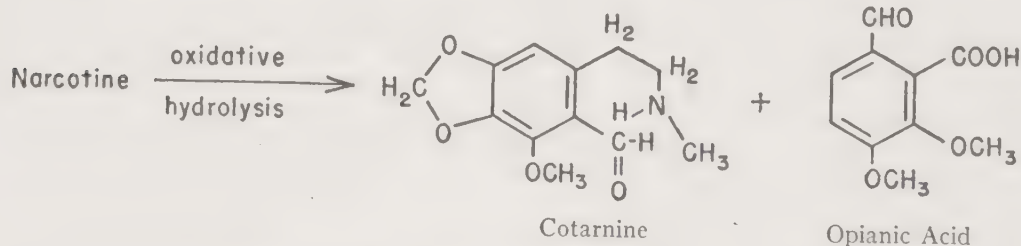
↓ HCl



Cotarnine Chloride

Cotarnine chloride occurs as a light-yellow powder which is deliquescent in moist air. It is soluble in water (1:1) and in anhydrous alcohol (1:4). Solutions may be sterilized by the application of heat.

This compound exerts an action on the uterus which is similar to that brought about

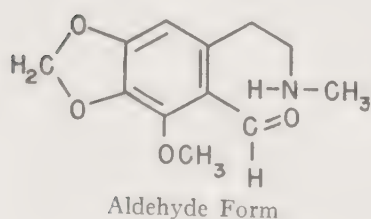


Cotarnine

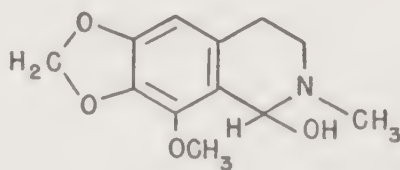
Opianic Acid

Cotarnine may exist in three possible forms (aldehyde, carbinol and quaternary) and there is some evidence in favor of each form. It is possible that it exists in all three forms in equilibrium.

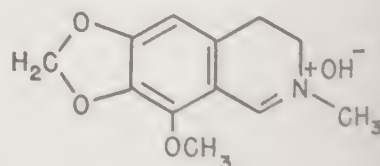
by hydrastine and hydrastinine. It causes increased uterine contractions and is utilized as a uterine hemostatic in certain hemor-



Aldehyde Form



Carbinol Form



Quaternary Form

rhagic conditions. It may be injected as a 10 per cent solution in urgent cases. It is applied externally in the undiluted form, as a strong solution or as impregnated (30 per cent) gauze or cotton to stop bleeding. This drug is not used to the extent that it was formerly and will probably be used less as time goes on.

The average dose is 60 mg.

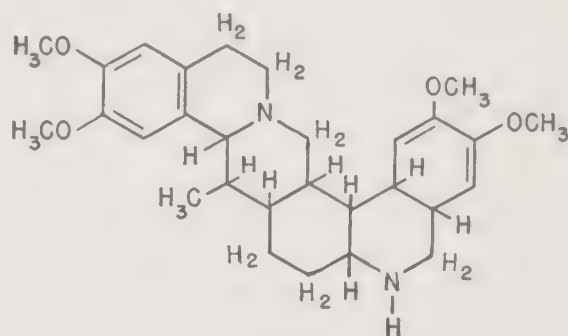
IPECAC AND THE IPECAC ALKALOIDS

The dried rhizome and roots of *Cephaelis Ipecacuanha* (Rio or Brazilian Ipecac) or *C. acuminata* (Cartagena, Nicaragua or Panama Ipecac) constitute the official drug known as "Ipecac." The U.S.P. requires that the crude drug contain at least 2 per cent of ether-soluble alkaloids. The two principal alkaloids of ipecac are emetine ($C_{29}H_{40}O_4N_2$) and cephaëline ($C_{20}H_{28}O_4N_2$), but there is no official requirement as to the ratio of these alkaloids in the drug. Ordinarily the Rio ipecac contains predominantly emetine, whereas the Cartagena ipecac has a greater ratio of cephaëline. Emetine is O-methylated cephaëline, and is the most important of the two from a medicinal standpoint.

Ipecac was of Brazilian origin and was first imported into Europe in 1658 as a treatment for dysentery. However, it was not until 1905 that it was realized the drug was effective only in amebic dysentery and not in bacillary dysentery. Ipecac has many disadvantages in the treatment of dysentery, not the least of these being its emetic and expectorant action, and it is rarely employed for that purpose in modern therapeutics. The expectorant and emetic properties of ipecac, however, are the basis of its principal uses today.

Emetine Hydrochloride U.S.P. The non-phenolic alkaloid, emetine, is obtained by isolation from natural sources or is obtained synthetically by methylating naturally occurring cephaëline (phenolic). Emetine is obtained from the crude drug by first extracting the total alkaloids with a suitable

solvent and then separating them by a method similar to that outlined for the separation of phenolic and nonphenolic bases (q.v.). The free base was first isolated by Pelletier and Caventou in 1817. Because of its complex structure, the alkaloid has not been totally synthesized, and the structure has been arrived at on the basis of degradative evidence.



Emetine

The free base is levorotatory and occurs as a water-insoluble, light-sensitive, white powder. It is soluble in alcohol or the immiscible solvents. It contains two basic nitrogens and forms salts quite readily. The hydrochloride is the salt officially recognized, and, as obtained by crystallization from water, its formula is



However, the U.S.P. merely sets limits for the water of hydration content (8 to 14 per cent). Other than the hydrochloride, the hydrobromide and the camphosulfonate (as a solution) are sometimes used.

The hydrochloride occurs as "a white or very slightly yellowish, odorless, crystalline powder." The salt is freely soluble in water (1:4) and in alcohol. Its solutions have an approximate pH of 5.5 but, when prepared for injection, they should be adjusted to a pH of 3.5. Sterilization of solutions may be effected by the intermittent method (Tyndallization) or by bacteriologic filtration.

As the name implies, emetine possesses emetic action due to its marked irritation of mucous membranes when ingested orally. However, it is used principally for its ame-

bicidal qualities. It was shown by Vedder (1911) that the drug was quite toxic to ameba in vitro. The following year, Rogers successfully employed the drug in treating amebic dysentery and hepatic amebiasis. However, considerable research has shown that, while emetine causes prompt recession of the symptoms of acute intestinal amebiasis, it cures only 10 to 15 per cent of the cases. The recession of symptoms quite often results in patients who, believing they are cured, become carriers. Therefore, emetine is probably best used for symptomatic control of acute amebic dysentery and should be supplemented by other more effective drugs. Emetine, however, is said by some investigators to be the only amebicide of value in amebic abscess or amebic hepatitis. It is administered subcutaneously or intramuscularly in a dose of 1 grain per day for 10 to 12 days.

The average daily intramuscular dose is 60 mg.

CURARE AND CURARE ALKALOIDS

Originally, *curare* was a term used to describe collectively the very potent arrow poisons used since early times by the South American Indians. These arrow poisons were prepared from numerous botanic sources and often were mixtures of several different plant extracts. Some were poisonous by virtue of a convulsant action and others by a paralyzant action. It is only the latter type which is of value in therapeutics, and which is ordinarily spoken of as "curare."

Chemical investigations of the various curares were not too successful because of the difficulties attendant upon obtaining authentic samples of curare from definite botanic sources. It was only in 1935 that King was able to isolate a pure crystalline alkaloid, which he named *d*-tubocurarine chloride, from a curare of unknown botanic origin.³¹ It was shown to possess, in great measure, the paralyzing action of the original curare. Wintersteiner and Dutcher,³²

in 1943, also isolated the same alkaloid. They, however, showed that the botanical source was *Chondodendron tomentosum* (Fam. *Menispermaceae*) and thus provided a known source of the drug.

Following the development of quantitative bio-assay methods for determining the potency of curare extracts, a purified and standardized curare was developed and marketed. More recently, *d*-tubocurarine chloride itself has appeared on the market.

Intocostrin N.N.R. (Standardized and Purified Curare Extract).

Intocostrin prepared from *Chondodendron tomentosum* extract is made by first extracting with alcohol a desiccated curare obtained from a heavy syrup of the bark and stems of *Chondodendron tomentosum*. The alcoholic extract is evaporated to dryness; a sterile filtered solution having a pH of 4.6 to 4.8 is made and adjusted to a standard potency of 20 units per cubic centimeter. The final solution contains sodium chloride 0.45 per cent and trichlorobutanol 0.5 per cent; sterilized by filtration and its pH again adjusted to 4.6 to 4.8.

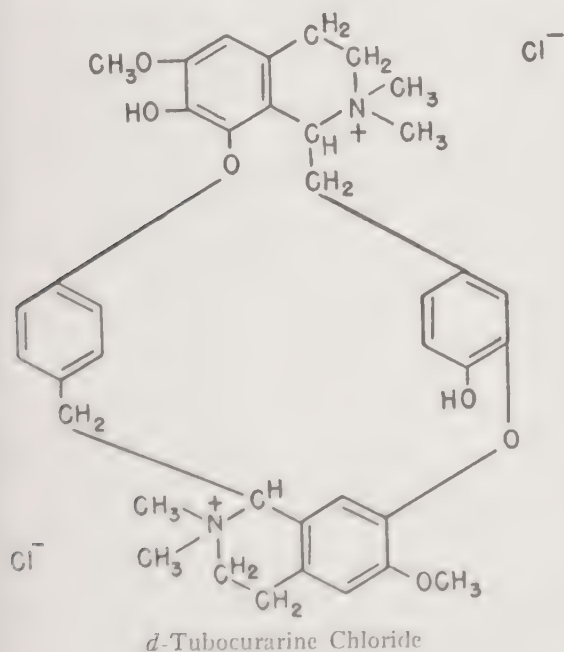
A "unit" is defined as possessing the same potency as 0.15 mg. of pure *d*-tubocurarine chloride. The drug is assayed by the "Head-Drop Crossover" method, a very accurate physiologic assay.

As previously indicated, curare is used for its paralyzing action on voluntary muscles, where it is probable that the site of action is the myoneural junction. Its action is inhibited by neostigmine, a physiologic antidote, which is used in cases of respiratory embarrassment due to overdosage. However, it is often necessary to use artificial respiration as an adjunct until the maximum curare action has passed. Curare is inactive orally, and when used therapeutically, it usually is injected intravenously.

It was first introduced as a muscle relaxant in shock therapy of mental disorders. By its use the incidence of bone and spine fractures and dislocations, often unavoidably resulting from the convulsions due to shock, has been reduced markedly. Following this usage it was employed, together with general anesthesia, to obtain complete muscular relaxation. Prior to its use, satisfactory mus-

cle relaxation in various surgical operations (e.g., abdominal surgery) was obtainable only with "deep" anesthesia using the ordinary general anesthetics. Curare, however, permits a lighter plane of anesthesia with no sacrifice in the muscular relaxation which is so important to the surgeon. In this connection, it is well to note that, when using ether, only one-third of the usual dose of curare is administered because ether itself has a curarelike action. Another recognized use of curare is in the diagnosis of myasthenia gravis, wherein it causes an exaggeration of symptoms in minute doses. It has been used to a limited extent in the treatment of spastic, hypertonic and athetoid conditions. One of its principal drawbacks in these conditions is its short duration of action. Its usefulness would be increased immeasurably if its action could be spread over a greater time period and, in the case of *d*-tubocurarine, steps have been taken to do this (q.v.). The dosage of the extract is variable for the different clinical applications, and it is advisable to consult the commercial literature on the product for dosage information.

***d*-Tubocurarine Chloride.** This alkaloid is prepared from crude curare by a process of purification and crystallization; it occurs as the pentahydrate.



The structural considerations have been investigated principally by King, and Wintersteiner and Dutcher. The structure given is that proposed by King.³¹

d-Tubocurarine chloride occurs as a white, crystalline powder, which is soluble in water. Chemically, it is a quaternary salt and solutions of it are stable to sterilization by heat.

This alkaloid is responsible for the activity of curare extracts, and constitutes one-half of the total solids in the purified curare extract (Intocostin). Because it is a pure, crystalline material, it may be standardized by weight as well as biologically. Three mg. of the compound are equivalent to 20 units (1 cc.) of Intocostin.

It may be used for the same conditions as the latter, and it has approximately the same duration of action. When injected intramuscularly, its action lasts longer than when given by the intravenous route. *d*-Tubocurarine chloride has found an increasing use in conjunction with intravenous pentothal anesthesia. Solutions containing the usual concentration of *d*-tubocurarine (3 mg./cc.) cause undesirable dilution and precipitation of the thiobarbiturate because of high acidity. To aid in overcoming this, more concentrated solutions (15 mg./cc.) with a lower acidity are used for this purpose. Because of its high potency, adequate care should be taken not to confuse this solution with the less potent one.

Recently, the alkaloid suspended in peanut oil with myricin (myricyl palmitate) has been used intramuscularly to slow down the absorption of the drug and in that way prolong its effect. By controlling the blood concentration of the alkaloid it is possible to obtain a partial blocking effect, whereby certain of the undesirable abnormal impulses are stopped without impairing voluntary movement. In this connection, it is of value in spastic, athetoid and hypertonic conditions when combined with retraining of the muscles during the period of quietude.

The dosage is the same as that of the purified extract.

QUINOLINE GROUP

CINCHONA AND THE CINCHONA ALKALOIDS

The bark of the cinchona tree (*Cinchona succirubra*, *C. Ledgeriana*, *C. Calisaya* and hybrids of these, Fam. *Rubiaceae*) has been known to possess medicinal virtues since its first purported use (1630) as an antimalarial in Peru. Shortly thereafter it was introduced into Europe by the Jesuit priests and since then has risen to a position of considerable eminence in the drug field. The development of cinchona from its origin as an uncultivated South American plant to its present-day cultivation in India and, particularly, Java is an interesting chapter in the history of the drug.³³ Its importance is attested by the Department of Commerce report that 1,270,551 lb. of cinchona bark were received in the United States in the eight month period ending August 1947.³⁴ Most of this supply came from the Dutch East Indies, but some was obtained also from Peru, Guatemala, Costa Rica and Colombia.

The crude drug contains numerous alkaloids, of which quinine, quinidine, cinchonine and cinchonidine are the most abundant and important. An average commercial yield of the cinchona alkaloids is about 4.9 per cent quinine, 0.1 per cent quinidine, 0.4 per cent cinchonidine and 0.3 per cent cinchonine. These alkaloids are all closely related in structure and medicinal action. Table 46 (page 449) shows the structural relationships using as a basic skeleton, 9-*rubanol*, which is derived from the parent compound, *ruban*. This nomenclature was proposed by Rabe to simplify the naming of this type of compound and to indicate their origin from the *Rubiaceae*.³⁵

Being a drug of great economic importance, quinine has been investigated extensively in an effort either to develop a synthetic substitute or to modify the structure of the natural alkaloid in such a manner as to improve its action. It was early shown that the stereochemical configuration had little effect on the antimalarial activity, but that certain structural changes had a pronounced effect. Activity was shown to decrease markedly when the secondary alcohol group was modified in any way. The entire quinuclidine nucleus was shown to be unnecessary for activity, but the α -aryl- β -tertiary amino alcohol system seems essential.³⁶ Other considerations, not within the scope of this text, are also of importance.

Aside from an antiparasmodial action, quinine has long been known to have an effect on the pneumococcus. The quaternary salts of cinchona bases are, reportedly, better antipneumococci than the free alkaloids.³⁷ For a discussion of this phase of its activity the reader is directed to the section dealing with cupreine and its derivatives.

Allergic skin reactions to therapeutic doses of quinine are not uncommon. A limited amount of research has shown that individuals who suffer from an idiosyncrasy to the levorotatory alkaloids of cinchona often show no sensitivity to the dextro isomers of those alkaloids. It is because of this remarkable allergic specificity that individuals who are using quinine as an antimalarial are able to change to the dextrorotatory quinidine upon occurrence of allergic manifestations.

A critical re-evaluation of the comparative antimalarial activities of the common cin-

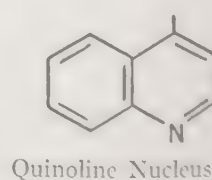
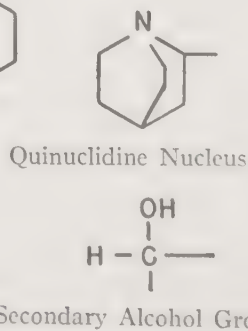
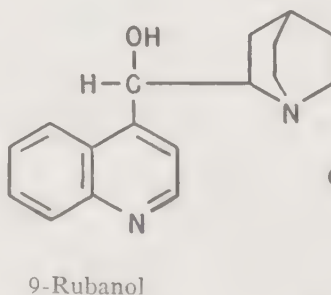
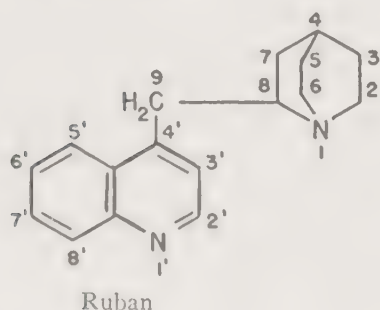


TABLE 46. STRUCTURAL RELATIONSHIP OF CINCHONA ALKALOIDS

COMPOUND	SUBST. IN 3 POSITION	SUBST. IN 9 POSITION	SUBST. IN 6' POSITION	CHEMICAL NAME
*Quinine & Quinidine (C ₂₀ H ₂₄ O ₂ N ₂)	—CH=CH ₂	—OH	—OCH ₃	6'-methoxy-3- vinyl-9-rubanol
*Cinchonine & Cinchonidine (C ₁₉ H ₂₂ ON ₂)	—CH=CH ₂	—OH	—H	3-vinyl-9- rubanol
Cupreine (C ₁₉ H ₂₂ O ₂ N ₂)	—CH=CH ₂	—OH	—OH	6'-hydroxy-3- vinyl-9-rubanol
Hydrocupreine (C ₁₉ H ₂₄ O ₂ N ₂)	—CH ₂ —CH ₃	—OH	—OH	6'-hydroxy-3- ethyl-9-rubanol

* Stereoisomers.

chona alkaloids during the early stages of World War II indicated that the relative effectiveness of each of them was roughly the same.³⁸ For this reason, the use of crude preparations of the alkaloids (e.g., totaquine) is on a rational basis in spite of the fact that they contain relatively small amounts of quinine.

Totaquine U.S.P. From the standpoint of economy, crude mixtures of the cinchona alkaloids have always been of interest. The earliest type was known as *quinetum* and contained a large proportion of quinine. As the interest in pure quinine increased, another type of crude mixture ("cinchona febrifuge"), composed of the alkaloids remaining after quinine removal, was introduced to replace quinetum. The Malaria Commission of the Health Section of the League of Nations has more recently introduced "totaquina." This was first accepted in the British Pharmacopoeia (1932), and then in the U.S.P. XII and XIII, the latter defining it as containing at least 10 per cent of quinine and a total of 70 to 80 per cent of crystallizable cinchona alkaloids.

Totaquine is used as an inexpensive anti-malarial drug. It possesses no advantages over quinine except that of cost.

The average dose is 0.6 Gm.

Quinine N.F. Quinine was first isolated by Pelletier and Caventou in 1819; they also showed that the alkaloids of cinchona were responsible for its febrifuge properties.

Much work was carried out in an effort to establish the structure of quinine, but major credit is due to Rabe and his co-workers who postulated the true structure. The total synthesis of quinine by Woodward and Doering,³⁹ although economically unfeasible, has corroborated Rabe's postulation.

Quinine is obtained from quinine sulfate prepared from the crude drug (q.v.). To obtain it from solutions of quinine sulfate, a solution of the sulfate is alkalinized with ammonia or sodium hydroxide. Another method is to pour an aqueous solution of quinine bisulfate into excess ammonia water with stirring. In either procedure, the precipitated base is washed and recrystallized. The pure alkaloid crystallizes with three molecules of water of crystallization. It is efflorescent, losing one molecule of water at 20° C. under normal conditions, and losing two molecules in a dry atmosphere. All water is removed at 100° C.

It occurs as a levorotatory, odorless, white crystalline powder possessing an intensely bitter taste. It is only slightly soluble in water (1:1,500), but it is quite soluble in alcohol (1:1), chloroform (1:1) or ether.

It behaves as a diacidic base and readily forms salts. These may be of two types, the "acid or bi-salts" or the "neutral" salts. The neutral salts are formed by involvement only of the tertiary nitrogen in the quinuclidine nucleus, and the "acid" salts are the result of involvement of both basic nitrogens. Inas-

much as the quinoline nitrogen is very much less basic than the quinuclidine nitrogen, involvement of both nitrogens results in a definitely acidic compound. The formulae and solubilities of the common official salts of quinine are given in Table 47. With regard to salts of quinine, although they may possess some advantageous features with respect to one another, the speed of absorption and subsequent therapeutic effect

and skin eruptions are collectively known as "cinchonism" and are best treated by discontinuing the drug. Quinine is noncumulative, a single dose being disposed of in approximately 24 hours. This is in contrast to such a drug as atabrine (quinacrine) which is cumulative. Quinine, therefore, is given frequently to maintain its blood level at an effective concentration. It has been demonstrated that a dose of quinine is at

TABLE 47. FORMULAE AND SOLUBILITIES OF THE COMMON OFFICIAL QUININE SALTS

QUININE SALT AND FORMULA	WATER	ALCOHOL	SOLUBILITY* CHLOROFORM	ETHER	GLYCERIN
Quinine Sulfate $B_2 \cdot H_2SO_4 \cdot 2H_2O \dagger$	810 35 (100° C.)	120 10 (80° C.)	Slightly	Slightly	
Quinine Bisulfate $B \cdot H_2SO_4 \cdot 7H_2O$	10 1 (100° C.)	25 1 (80° C.)	625		15
Quinine Hydrochloride $B \cdot HCl \cdot 2H_2O$	16 0.5 (100° C.)	1	1	350	7
Quinine Dihydrochloride $B \cdot 2HCl$	0.6	12	Slightly	Very Slightly	
Quinine Hydrobromide $B \cdot HBr \cdot H_2O$	40 3.2 (80° C.)	1	1	25	7
Quinine Phosphate $B_3 \cdot 2H_3PO_4 \cdot 5H_2O$	600	60 (80° C.)			
Quinine Salicylate $B \cdot C_6H_4(OH)(COOH) \cdot H_2O$	Slightly	15	25	160	13
Quinine and Urea Hydrochloride $B \cdot HCl \cdot CO(NH_2)_2 \cdot HCl \cdot 5H_2O$	1	3			
Quinine Ethylcarbonate $C_{23}H_{28}N_2O_4$	Slightly	3	1	10	

* The solubilities given in this table, unless so indicated, represent the number of cc. of solvent required to dissolve 1 Gm. of the salt at a temperature of 25° C.

† The letter "B", as used in the formulae given above, represents the quinine base, $C_{20}H_{24}O_2N_2$.

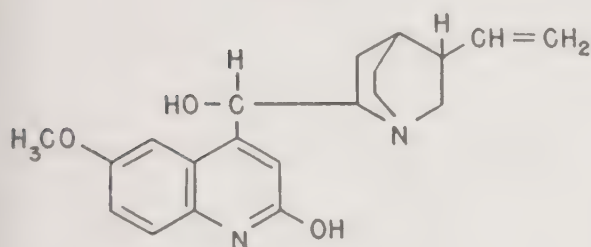
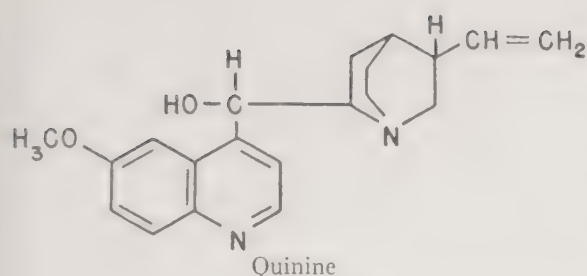
seems to be little influenced by the solubility of the compound.⁴⁰

The principal use of quinine and its salts is in the prophylaxis and treatment of malaria. Although newer antimalarials (e.g., atabrine, chloroquine, paludrine, etc.) are undoubtedly improvements on quinine, the latter drug will probably continue for some time as an important antimalarial. Quinine is not highly toxic and is effective in most types of malarial infection. Toxic symptoms such as tinnitus, vertigo, visual disturbances

least partly oxidized in the liver to the carbostyryl derivative (2'-hydroxy-6'-methoxy-3-vinyl-9-rubanol).⁴¹

This observation has provided an avenue of profitable research in prolonging the effect of quinine, this being accomplished by inserting less easily oxidized groups (e.g., phenyl) in the 2' position, together with other minor changes.

Quinine holds a position of some esteem as an oxytocic in combination with castor oil, although it is not always effective. Aside



from the uncertainty of action, the oxytocic use of quinine is attended by toxic dangers to both the mother and fetus.

Lesser uses of quinine are as an antipyretic, as a test agent in the diagnosis of myasthenia gravis (accentuates the symptoms), as a local anesthetic, as an antiseptic, and for numerous miscellaneous uses.

The average dose is 1 Gm.

OFFICIAL OCCURRENCE	PER CENT QUININE
N.F.	
Compound Hypophosphites Syrup. . . .	0.11

Quinine Sulfate U.S.P. Quinine sulfate is a very common salt of quinine and, is ordinarily, the "quinine" asked for by the layman.

It is prepared in one of two ways, i.e., from the crude bark or from the free base. When prepared from the crude bark, the powdered cinchona is alkalinized and then extracted with a hot, high-boiling petroleum fraction to remove the alkaloids. By carefully adding diluted sulfuric acid to the extract, the alkaloids are converted to sulfates, the sulfate of quinine crystallizing out first. The crude alkaloidal sulfate is decolorized and recrystallized to obtain the article of commerce. Commercial quinine sulfate is not pure but contains from 2 to 3 per cent of

impurities, which consist mainly of hydroquinine and cinchonidine.

To obtain quinine sulfate from the free base, it is neutralized with dilute sulfuric acid. The resulting sulfate, when recrystallized from hot water, forms masses of crystals with the approximate formula $(C_{20}H_{24}O_2N_2)_2 \cdot H_2SO_4 \cdot 8H_2O$. This compound readily effloresces in dry air to the official dihydrate, which occurs as fine, white needles of a somewhat bulky nature.

Quinine sulfate is often prescribed in liquid mixtures. From a taste standpoint, it is better to suspend the salt rather than to dissolve it. However, in the event that a solution is desired, it may be accomplished by the use of alcohol or, more commonly, by addition of a small amount of sulfuric acid to convert it to the more soluble bisulfate. The capsule form of administration is the most satisfactory for masking the taste of quinine when it is to be administered orally.

The uses of quinine sulfate are the same as those for quinine itself.

The average dose is 0.6 Gm.

OFFICIAL OCCURRENCE	PER CENT QUININE SULFATE
N.F.	
Cinchona Alkaloids Elixir. . . .	0.2

Quinine Bisulfate U.S.P. This salt of quinine is prepared by adding a mole of sulfuric acid to each mole of quinine sulfate which is suspended in water. The resulting solution then is concentrated until crystallization to quinine bisulfate takes place.

It occurs as a white, crystalline powder possessing a bitter taste. It is efflorescent and is affected by light. It dissolves readily in water to give solutions with an approximate pH of 3.5.

Quinine bisulfate has the same uses as quinine and quinine sulfate, but possesses a greater solubility which makes it desirable for some purposes. Occasionally, it is necessary to use quinine bisulfate in place of quinine sulfate, but one should bear in mind that the bisulfate contains only 59.12 per cent of anhydrous quinine, whereas the sulfate contains 82.86 per cent.

Other than for the usual quinine uses, quinine bisulfate is used as an antiseptic in the treatment of trachoma. It is used in 10 per cent solution for direct ophthalmic instillation or as a 2 to 4 per cent ophthalmic ointment. It is useful in all stages of the infection.

The average dose is 1 Gm.

Quinine Hydrochloride U.S.P. The appearance of this alkaloidal salt is very much like that of quinine sulfate. It effloresces in dry air. Solutions are neutral to litmus.

Because of its solubility, it is useful for intravenous or intramuscular injection. Care should be exercised, however, due to the possibility of necrosis at the site of injection. It has the same uses as other quinine salts and, in addition, it is used as a sclerosing agent for varicose veins.

The average dose is 0.6 Gm. (orally) and 0.2 Gm. (intramuscularly).

OFFICIAL OCCURRENCE	PER CENT QUININE HYDROCHLORIDE
U.S.P.	
Quinine and Urethane Injection	67.0 (approx.)
N.F.	
Compound Glycerophosphates	
Elixir	0.0875
Iron, Quinine and Strychnine	
Elixir	0.8

Quinine Dihydrochloride U.S.P. This salt is prepared from a solution of quinine bisulfate by treating it with barium chloride and concentrating the filtrate to crystallization.

It occurs as white, odorless, bitter crystals which are exceptionally soluble in water. Solutions have an approximate pH of 2.6. Because of its great solubility in water, this salt is useful for intravenous injection, although the acidity causes considerable irritation. Sterilization of solutions is effected by heating at 100° C. for 30 minutes or by other suitable procedures.

The uses of this salt conform to those of quinine.

The average dose is 1 Gm.

Quinine Hydrobromide N.F. Quinine

hydrobromide is prepared by neutralizing quinine with hydrobromic acid.

The salt occurs as odorless, white, silky needles which possess a bitter taste. It is sensitive to light.

Its uses are similar to those of quinine. It has been claimed that this salt may be utilized where a calming effect is desired, e.g., in nervous and cardiac patients, but the bromine content seems to be too low to exert any pronounced effect.

The average dose is 0.3 Gm.

Quinine Phosphate N.F. Because quinine phosphate is relatively insoluble in water, it is prepared by treating an aqueous solution of quinine hydrochloride with an aqueous solution of sodium phosphate. It also may be prepared by treating the alkaloid with diluted phosphoric acid.

This salt occurs as an efflorescent, white, crystalline powder. Its uses are exactly the same as those of quinine sulfate. Its principal reason for being official is its occurrence in Iron, Quinine and Strychnine Phosphates Elixir as a bitter tonic.

The average dose is 0.3 Gm.

OFFICIAL OCCURRENCE	PER CENT QUININE PHOSPHATE
N.F.	
Iron, Quinine and Strychnine Phosphates Elixir	0.5

Quinine Salicylate N.F. This salt, like the phosphate, is quite insoluble in water. Advantage is taken of this fact in its preparation by causing solutions of sodium salicylate and quinine sulfate to react, yielding a precipitate of the salicylate.

The uses of this salt are those of quinine, although it may exert some analgesic action due to the salicylic acid portion of the molecule. It has, on this basis, been used in rheumatic conditions, lumbago, influenza and related ailments.

The average dose is 0.3 Gm.

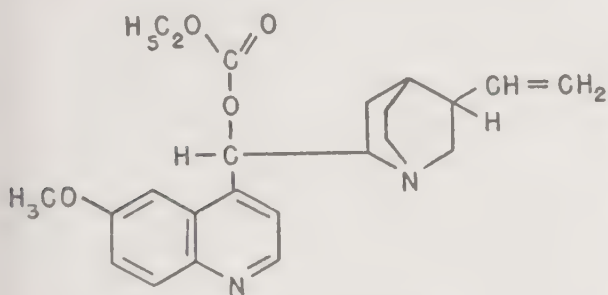
Quinine and Urea Hydrochloride N.F. This double salt of quinine and urea hydrochlorides may be made by treating a mole of quinine hydrochloride with a mole each of HCl and urea.

It is odorless and occurs in the form of colorless, translucent prisms or as a white granular powder. Because of its high solubility in water, it is suitable for injections.

It is used parenterally in treating malaria and also has been used for its local anesthetic effect on the cornea. It causes no mydriasis. Another widespread use of this double salt is in the sclerosing of veins, where its local anesthetic action coupled with the sclerosing action makes it a suitable agent. It is used in a 5 per cent solution. The main disadvantages as a sclerosing agent are its acidity and the possibility of sufficient quinine absorption to bring about "cinchonism."

The average dose is 0.5 Gm.

Quinine Ethylcarbonate (Euquinine)
N.F. This compound, strictly speaking, is not a quinine salt. It is included here as a matter of convenience. Quinine ethylcarbonate may be prepared by treating quinine with ethyl chlorocarbonate ($\text{ClCOOC}_2\text{H}_5$).



Quinine Ethylcarbonate

It occurs "as white, fine, soft needles, usually matted together in fleecy masses" and is odorless and almost tasteless. It is only slightly soluble in water but is readily soluble in dilute acids.

This compound is suitable as an anti-malarial and tonic and, in addition to being almost tasteless, is said to cause less severe cinchonism than does the sulfate. It lends itself to administration to young children who object to the bitter taste and are unable to swallow capsules.

The average dose is 1 Gm.

Quinine and Urethane Injection U.S.P.
This solution is made from approximately 2

parts of quinine hydrochloride and 1 part of urethane dissolved in water. The usual solution is neutral and contains 0.25 Gm. of the hydrochloride and 0.12 Gm. of urethane in 2 cc. The solution is sterilizable in an autoclave and is suitable for subcutaneous, intravenous or intramuscular injection. Its principal uses are for sclerosing veins and as a local anesthetic.

Quinidine. This alkaloid from cinchona is structurally identical with quinine and is diastereoisomeric with it. The close relationship existing between the two alkaloids is shown by the fact that oxidation of the secondary alcohol group results in the same ketone from each alkaloid.

This alkaloid is obtained from various cinchona species, from *Remijia pedunculata*, or it is made from quinine. Most of the quinidine used in the United States is obtained from natural sources. Less than 1 per cent of the alkaloid is obtainable from cinchona bark. It is prepared from the mother liquors of quinine sulfate production. These are treated with sodium hydroxide to obtain a precipitate, which then is extracted with ether to dissolve out the quinidine together with cinchonidine. To separate this mixture it is solubilized with sulfuric acid, neutralized with ammonia and finally treated with potassium and sodium tartrate to precipitate the insoluble cinchonidine tartrate. The quinidine in the mother liquor is precipitated as the difficultly soluble hydriodide, using potassium iodide as the precipitating agent. The hydriodide is neutralized, and the alkaloid is crystallized from alcohol. The quinidine of commerce contains approximately 20 per cent of dihydroquinidine. Studies⁴² have indicated that, although the dihydro form is more toxic than quinidine, it also has a greater antifibrillating action.

This alkaloid has much the same physical appearance and properties as quinine. It is, however, dextrorotatory. It contains two basic nitrogens and forms two series of salts in the same way as quinine. The hydriodide, as previously indicated, is sparingly soluble

(1:1,250 at 15° C.) in water and precipitates upon addition of potassium iodide to solutions of quinidine salts. In contrast to quinine, it forms a soluble neutral sulfate.

Although quinidine is as effective an antimalarial as quinine, it is not so used except where an individual has an idiosyncrasy to the levorotatory form (quinine). More generally, it is used as a cardiac drug in the treatment of auricular fibrillation. This is reflected by the fact that out of a total estimated requirement of 645,000 ounces in the United States for the 11 month period ending with June 1948, 517,000 ounces were destined for cardiac needs. Its action is to restore the fibrillating heart to a normal rhythm, the mechanism probably being a lessening of cardiac muscle irritability, the prolongation of the refractory period and the retardation of conduction in the muscle. Because the effect in retarding conductivity is greater than the effect on the refractory period, the drug causes extinction of the numerous uncontrolled stimuli, thus bringing the heart back to a normal rhythm.

The therapeutic benefit is not without danger to the patient who has had a fibrillation of long standing. This is due to the fact that the more forceful normal beat may dislodge an embolus with possible fatal consequences. Sensitivity to quinidine is not uncommon.

Quinidine Sulfate U.S.P. This salt, $(C_{20}H_{24}O_2N_2)_2 \cdot H_2SO_4 \cdot 2H_2O$, is prepared by neutralizing the free alkaloid with diluted sulfuric acid. It crystallizes from water as the dihydrate. It occurs "as fine, needle-like, white crystals, frequently cohering in masses." It has a bitter taste and is affected by light.

It is somewhat soluble in water (1:100, 1:15 at b.p.), more soluble in alcohol (1:10) and in chloroform, but is almost insoluble in ether. Aqueous solutions are neutral or slightly alkaline in reaction.

This salt is the favorite means of administering quinidine because it is more soluble than the free base. It is used in the same

manner and for the same purposes as the free base.

The average dose is 0.2 Gm.

Cinchonidine Sulfate N.F. This salt, $(C_{19}H_{22}ON_2)_2 \cdot H_2SO_4 \cdot 3H_2O$, is the sulfate of the levorotatory alkaloid, cinchonidine, which is obtained from the quinine mother liquors (see quinidine manufacture). The cinchonidine is precipitated as a tartrate, as indicated, and is recovered from the precipitate by dissolving it in dilute acid and pouring this into excess ammonia. The precipitated base is treated with diluted sulfuric acid and converted to the neutral sulfate, which is recrystallized.

The sulfate occurs as efflorescent, white, silky acicular crystals which are soluble in water (1:65, 1:22 at 80° C.) and in alcohol (1:90, 1:41 at 60° C.), but not very soluble in chloroform or ether. It is light-sensitive.

Chemically, it is similar to quinine, possessing two basic nitrogens; it gives two series of salts, the acid and neutral. It gives an insoluble tartrate when treated with soluble tartrates, and this forms the basis for a test used to distinguish between cinchonidine and cinchonine. Cinchonine does not form an insoluble tartrate. This alkaloid, together with cinchonine, fails to give the thalleioquin test, which distinguishes it from quinine and quinidine.

As previously indicated, cinchonidine is useful as an antimalarial in a manner similar to quinine. It is said to be more apt to cause epileptiform convulsions than is quinine when used in high doses.

The average dose is 0.15 Gm.

OFFICIAL OCCURRENCE	PER CENT
	CINCHONIDINE SULFATE
N.F.	
Cinchona Alkaloids Elixir	0.1

Cinchonine Sulfate N.F. The alkaloid, cinchonine, is obtained from the quinine mother liquors by precipitating all of the remaining alkaloids (chiefly cinchonine, cinchonidine and quinidine) with alkali. Because cinchonine is comparatively insoluble in ether, it remains as a residue when the

crude alkaloidal precipitate is extracted with ether. This residue may be recrystallized from alcohol to free it of quinidine. Dihydrocinchonine, another impurity, is removed by precipitating the cinchonine base as the cuprichloride, which is later decomposed to liberate the free alkaloid.

The sulfate, $(C_{19}H_{22}ON_2)_2 \cdot H_2SO_4 \cdot 2H_2O$, is prepared by neutralizing the free alkaloid with dilute sulfuric acid and crystallizing. It occurs as colorless, lustrous, very bitter crystals. It is soluble in water (1:60, 1:33 at 80° C.), alcohol (1:12.5, 1:7 at 60° C.) or chloroform (1:47), but not very soluble in ether. Aqueous solutions are almost neutral in reaction.

Cinchonine is used for the same purposes as quinine. Being dextrorotatory, it is of value, as is quinidine, in treating patients who display a sensitivity to the levorotatory cinchona alkaloids.

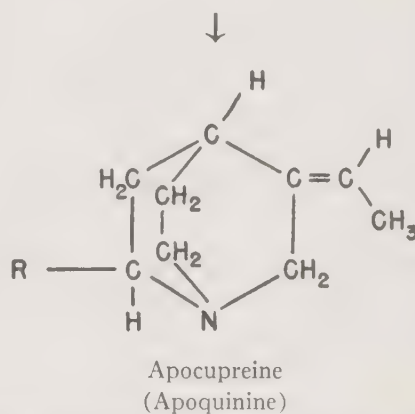
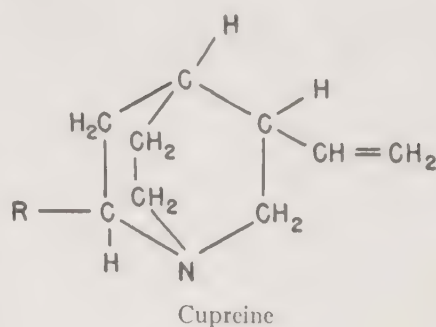
The average dose is 0.15 Gm.

OFFICIAL OCCURRENCE	PER CENT
N.F.	CINCHONINE SULFATE
Cinchona Alkaloids Elixir	0.1

CUPREA BARK ALKALOIDS

Cupreine. Closely related to cinchona, the plant *Remijia pedunculata* furnishes "cuprea bark," which contains numerous alkaloids. The most important of these are quinidine and cupreine, $C_{19}H_{22}O_2N_2$. The latter occurs in the form of a molecular complex with quinine, $C_{20}H_{24}O_2N_2 \cdot C_{19}H_{22}O_2N_2 \cdot 4H_2O$, when isolated. Since cupreine is an O-demethylated quinine (see Table 46), it has phenolic properties and is thus separated from the quinine (nonphenolic) in the complex on the basis of its solubility in aqueous sodium hydroxide solution. That it is closely related to quinine is shown by the fact that O-methylation yields quinine. However, O-demethylation of quinine with acids or alkalies does not yield the expected cupreine, but an isomer of it. This product has been variously termed *apoquinine*, *apocupreine* and *β-isocupreine*. The change in structure takes place at the vinyl group, where this

group isomerizes to the alkylidene type of radical.



(R = the remainder of the molecule with the exception of the quinuclidine nucleus.)

The alkaloid, cupreine, is not particularly important in therapeutics. Dihydrocupreine,* however, which is obtained by catalytically reducing cupreine or by demethylating dihydroquinine with strong hydrochloric acid (the usual process), is therapeutically important. It is the basis of ethyl hydrocupreine and related products. Likewise, the O-alkylated derivatives of apocupreine are of great interest. All of these derivatives are an outgrowth of the desire to obtain an antipneumococcic drug, and the importance of this field of investigation would have been paramount had not the sulfa drugs and penicillin stepped in to eclipse them.

It was in 1911 that Morgenroth introduced the ethyl substituted dihydrocupreine known as *optochin* (optoquine). This compound showed a remarkable specificity for

* The terms "dihydrocupreine" and "hydrocupreine" are synonymous.

the pneumococcus, and soon the whole series was investigated. The ethyl derivative is most effective against the pneumococcus and the octyl derivative against *B. diphtheriae* and staphylococcus. There is little difference in the activity of the *n*-octyl and the iso-octyl derivatives, and the latter is found as the commercially occurring "vuzin." The greatest drawback to the use of these compounds was the tendency toward causing damage to the optic nerve. Because of this toxicity, other compounds were sought, among which was β -hydroxyethyl hydrocupreine. This compound was shown to be one-fourth as active as optochin, but its toxicity was much lower in proportion. The ethyl ether of apocupreine was also shown to be quite active and much less toxic than optochin, but it still retained some of its eye-damaging properties. Detoxification of the ethyl ether of apocupreine by the introduction of an alcoholic hydroxyl in the β -position of the ethyl group gave β -hydroxyethyl apocupreine. This drug appeared to be the most promising in that it was quite effective as an antipneumococcic and was not toxic to the eye. It would undoubtedly have enjoyed clinical use except for the advent of the sulfa drugs.

Ethylhydrocupreine Hydrochloride N.F. (Optochin Hydrochloride, Optoquine Hydrochloride). This derivative of dihydrocupreine is obtained by the ethylation of the free phenolic hydroxyl group.

It occurs "as a white or light yellowish white, odorless, crystalline powder, having a very bitter taste."

The salt, $C_{21}H_{28}O_2N_2 \cdot HCl$, is quite soluble in water (1:2), in alcohol (1:5) and in chloroform (1:2.5), but is almost insoluble in ether.

It gives the thalleioquin test (as does cupreine), but may be distinguished from cupreine by its insolubility in aqueous alkali hydroxide solutions.

This compound was introduced into medicine as an antipneumococcic. It soon became evident that it was unsuitable because it caused damage to the optic nerve. However,

with due care exercised, it is suitable for local application in the eye in pneumococcic infections because of its remarkably specific action on most types of pneumococci. As an illustration of its specificity, the British Pharmaceutical Codex (1934) states that it kills the pneumococcus in a dilution of 1:400,000 in vitro but requires concentrations of 100 to 1,000 times stronger to kill other bacteria in a comparable manner. It is used ophthalmically in a 1 to 2 per cent aqueous solution.

Isoamylhydrocupreine (Eucupin). This compound, $C_{24}H_{34}O_2N_2$, is used principally as the dihydrochloride. The free base occurs as a fine, white, water-soluble powder, whereas the dihydrochloride occurs as fine, white needles which are soluble (1:15) in water.

It has been infrequently used internally as the free base (for slow absorption) in the treatment of malaria, sepsis and influenza. It finds its main application, however, externally as an antiseptic (usually 1:200 solution) and local anesthetic in dentistry and medicine. This compound is a stronger local anesthetic than cocaine. As an antiseptic it is more effective than quinine against protozoa and bacteria.

Iso-octylhydrocupreine Dihydrochloride (Vuzin Dihydrochloride).

This compound occurs as a white, crystalline powder which is readily soluble in water, alcohol or chloroform. Solutions are acidic and should not be made with physiologic saline solution or with alkaline substances. Because the solutions are not indefinitely stable, they should be freshly made. However, they may be sterilized by the application of heat.

It is a powerful bactericide and is used externally in solution (one-half to one per cent) as a disinfectant for wounds or following the incision of boils, abscesses, carbuncles and similar conditions.

INDOLE GROUP

YOHIMBE AND THE YOHIMBE ALKALOIDS

The bark of *Pausinystalia yohimba* (also known as *Corynanthe yohimbe*) contains

numerous alkaloids. Among these are yohimbine, isoyohimbine, dihydroyohimbine, alloyohimbine and other bases. The chief alkaloid, from a therapeutic standpoint, is yohimbine, and the value of Yohimbe lies in its being a source of the alkaloid.

Yohimbine (Quebrachine, Aphrodine). Yohimbine, $C_{21}H_{26}O_3N_2$, is obtained from the bark of Yohimbe by numerous methods of isolation. The free base occurs as water-insoluble but alcohol-soluble, colorless needles. It is a mono-acidic base and readily forms salts of which the hydrochloride, $C_{21}H_{26}O_3N_2 \cdot HCl$, is the most important. The hydrochloride is water-soluble (1:120) and gives practically neutral solutions which may be heat sterilized.

This alkaloid is used principally as an aphrodisiac, although its use in this capacity is open to serious question. Its value as an aphrodisiac is said to be due to the increase of reflexes in the pelvic region. Although promoted for human use also, it finds its principal application in the veterinary field. Its suggested dose is from 3 to 8 mg. given

hypodermically (0.5 per cent solution) or orally.

ERGOT AND THE ERGOT ALKALOIDS

Ergot consists of the dried sclerotium of *Claviceps purpurea*, Fam. *Hypocreaceae*, a fungus which develops on the rye plant. It has been shown⁴³ that hosts other than rye can produce a comparable ergot.

Recorded accounts of the poisonous nature of ergot extend back to early times, chiefly as a result of gangrene (Holy Fire, St. Anthony's Fire) caused by ingestion of bread made from ergot-infested rye. The gangrene was a direct result of the peripheral vasoconstriction produced by ergot. The oxytocic action of ergot was recognized as early as the sixteenth century and was used by midwives for years prior to its acceptance by the medical profession.

Although ergot contains numerous constituents, it is believed that its principal pharmacologic actions can be accounted for by its alkaloidal content. Of the alkaloids present (see Table 48) in ergot, only the levorotatory ones show significant physiologic activity.

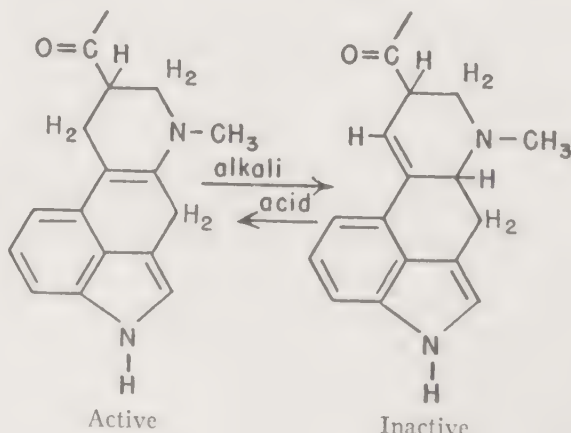
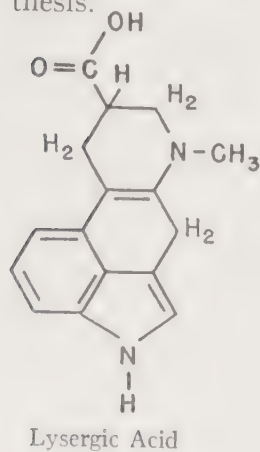
TABLE 48. ALKALOIDS OF ERGOT*

ACTIVE	$\left[\alpha \right]_D^{t^0}$	
	in $CHCl_3$	
Ergotoxine $C_{35}H_{39}O_5N_5$ —197	$\left\{ \begin{array}{l} \text{Ergocristine } C_{35}H_{39}O_5N_5 \text{ —186} \\ \text{Ergocryptine } C_{32}H_{41}O_5N_5 \text{ —187} \\ \text{Ergocornine } C_{31}H_{39}O_5N_5 \text{ —188} \end{array} \right.$	
Ergotamine $C_{33}H_{35}O_5N_5$ —155		
Ergosine $C_{30}H_{37}O_5N_5$ —161		
Ergocristine $C_{35}H_{39}O_5N_5$ —186		
Ergonovine $C_{19}H_{23}O_2N_3$ —16		
INACTIVE	$\left[\alpha \right]_D^{t^0}$	
	in $CHCl_3$	
Ergotinine $C_{35}H_{39}O_5N_5$ +365	$\left\{ \begin{array}{l} \text{Ergocristinine } C_{35}H_{39}O_5N_5 \text{ +366} \\ \text{Ergocryptinine } C_{32}H_{41}O_5N_5 \text{ +408} \\ \text{Ergocorninine } C_{31}H_{39}O_5N_5 \text{ +409} \end{array} \right.$	
Ergotaminine $C_{33}H_{35}O_5N_5$ +385		
Ergosinine $C_{30}H_{37}O_5N_5$ +420		
Ergocristinine $C_{35}H_{39}O_5N_5$ +366		
Ergometrine $C_{19}H_{23}O_2N_3$ +414		

* Reproduced from an article on ergot in *Research Today*, Indianapolis, Eli Lilly, 3:53, 1946.

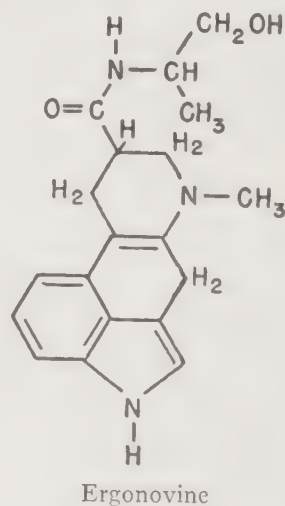
As will be noted, Table 48 shows that ergotoxine is not a chemical entity, in accordance with Stoll's work in 1943. He showed that ergotoxine was composed of three active levorotatory components, namely, ergocristine, ergocryptine and ergocornine. Further inspection of Table 48 shows that the ergot alkaloids occur as diastereoisomeric pairs. The members of each pair are interconvertible upon proper treatment, probably differing in the lysergic acid portion of the molecule (see below). For many years the activity of ergot was thought to reside in the water-insoluble fraction. However, in 1932, Moir called attention to the fact that the water-soluble fraction also exhibited a stimulant action on the uterus. By 1935, the active alkaloid in the water-soluble fraction was isolated almost simultaneously by four research groups, and is the alkaloid we now know as ergonovine (ergometrine in Great Britain).

Little was known of the structure of the ergot alkaloids until some fifteen years ago. We are largely indebted to Craig and Jacobs of the Rockefeller Institute for Medical Research and to Stoll of Switzerland for the present-day structural knowledge of these alkaloids. It had been known for some time that the ergot alkaloids yielded, among other products, a 16 carbon atom nucleus, ammonia and a keto acid. This 16 carbon atom nucleus was termed lysergic acid and was common to all of the alkaloids. Its structure has been the object of intensive research and the formula given below is believed to account for all of its properties, although this structure has not been proven by synthesis.



Lysergic acid is connected through an amide linkage to the rest of the alkaloidal molecule, which consists largely of amino acid residues, ammonia and keto acids. The occurrence of amino acids among the hydrolytic products of the ergot alkaloids is unusual and is of considerable biochemical interest. The possibility that the amino acids exist in a peptide linkage may explain some of the peculiar proteinlike properties exhibited by this group. Table 49 (page 459) shows the fragments obtained by degradation of the various alkaloids.

At the present state of our knowledge, accepting the structure of lysergic acid as postulated, it is possible to reconstruct only ergonovine with accuracy. This is because it is composed only of *d*-2-aminopropanol and lysergic acid. Constructions of other alkaloids have also been made, but are a matter of conjecture and, hence, will not be illustrated.



More recently, synthetic derivatives of the ergot alkaloids have appeared on the scene

(Proposed by
Craig & Jacobs⁴⁴)

TABLE 49. FRAGMENTS OBTAINED BY DEGRADATION OF ERGOT ALKALOIDS*

ERGOSINE	→	<i>l</i> -Leucine + Pyruvic acid + <i>d</i> -Proline + NH ₃ + Lysergic acid
ERGOTAMINE	→	<i>l</i> -Phenylalanine + Pyruvic acid + <i>d</i> -Proline + NH ₃ + Lysergic acid
ERGOCRISTINE	→	<i>l</i> -Phenylalanine + Isobutyrylformic acid + <i>d</i> -Proline + NH ₃ + Lysergic acid
ERGOTOXINE	{	Ergocryptine→ <i>l</i> -Leucine + Isobutyrylformic acid + <i>d</i> -Proline + NH ₃ + Lysergic acid
		Ergocornine→ <i>l</i> -Valine + Isobutyrylformic acid + <i>d</i> -Proline + NH ₃ + Lysergic acid
		Ergocristine→ <i>l</i> -Phenylalanine + Isobutyrylformic acid + <i>d</i> -Proline + NH ₃ + Lysergic acid
ERGONOVINE	→	<i>d</i> -2-Aminopropanol + Lysergic acid

* Reproduced from an article on ergot in *Research Today*, Indianapolis, Eli Lilly, 3:55, 1946.

and appear to possess desirable properties not obtained from the naturally occurring drug. The chief derivatives in this category are Dihydroergotamine and Methergine (q.v.).

Pharmacologically, a division of ergot alkaloids may be made into the ergotoxinelike group (water-insoluble), consisting of ergotoxine and ergotamine, and the ergonovine group (water-soluble), of which ergonovine is the prime example.

The water-insoluble group has a strong stimulating action on the uterus, which is somewhat slower to appear than that elicited by ergonovine but is of longer duration. This group, unlike ergonovine, produces a rise in blood pressure because of peripheral constriction of the blood vessels. This constriction is due to a direct stimulation of the smooth muscle. It seems fairly evident that the chief offender, insofar as ergotism is concerned, is the ergotoxine group because of this constrictive effect. Of the two alkaloids in this group, the ergotamine is only about two-thirds as powerful as the ergotoxine, but is approximately one-half as toxic.

Ergonovine, the only active representative of the water-soluble group, has less of a paralyzing effect on the sympathetic nerve endings than does ergotoxine and, in fact, may be considered to be a sympathomimetic. It, however, is not a true sympathomimetic because it fails to raise the blood pressure upon intravenous injection. As indicated, it possesses a strong, prompt, stimulating ac-

tion on the uterus, particularly when gravid or at term. Although ergonovine can exert a peripheral constrictive action, no cases have yet been reported of ergotism due to its use. It is highly active orally and causes little nausea or vomiting.

Some physicians feel that none of the individual ergot alkaloids offers the advantages of mixtures of the alkaloids. For this reason, preparations containing a mixture of ergotamine and ergonovine (Neogynergen) or else the total alkaloids of ergot (Ergaloid) have been introduced into therapeutics. In effect, their principal advantage is a fast onset of action due to the ergonovine content coupled with a longer duration of action due to the water-insoluble alkaloid or alkaloids present.

Ergonovine Maleate U.S.P. This water-soluble alkaloid was isolated, as indicated, from ergot, in which it occurs to the extent of 0.2 mg. per Gm. of ergot. The several research groups which isolated the alkaloid almost simultaneously each named the alkaloid according to their own dictates. Thus, the names *ergometrine*, *ergotocin*, *ergostetrine* and *ergobasine* were assigned to this alkaloid. To clarify the confusion, the Council on Pharmacy and Chemistry of the A. M. A. adopted a new name, *ergonovine*, which is in general use today. Of course, commercial names still differ from the Council accepted name, the principal ones being Ergotrate (ergonovine maleate) and Basergin (ergonovine tartrate).

Isolation of the alkaloid is based upon the difference in its water solubility from that of the other accompanying free alkaloids. An extract is made with an immiscible solvent of the crude alkalized ergot. The solvent is removed from this extract, and the residue is dissolved in acetone, which is miscible with water. Upon dilution of the acetone solution with water, only the ergonovine remains in solution and is easily recovered.

The free base occurs as levorotatory, white crystals. It is quite soluble in water or alcohol. It readily forms crystalline, water-soluble salts, behaving in this respect as a mono-acidic base. The nitrogen involved in salt formation, obviously, is not the one in the indole nucleus since it is much more aromatic in character than the other nitrogen. The salt which is officially accepted and is on the market is the maleate, $C_{19}H_{23}O_2N_3 \cdot H_2C_4H_2O_4$. It is said to be a convenient form in which to crystallize the alkaloid and is also quite stable. The alkaloid is also marketed as the tartrate and hydracrylate. The latter (Ergotrate-H) is obtainable only in the form of an ampule solution and is used for intravenous and intramuscular injection.

Ergonovine maleate occurs in the form of a light-sensitive, white or nearly white, odorless, crystalline powder. It is soluble in water (1:36) and in alcohol (1:136), but is insoluble in ether and in chloroform.

Ergonovine has a powerful stimulating action on the uterus and is used for this effect. Since it seems to exercise a much greater effect on the gravid uterus than on the non-gravid one, it is safely used in small doses with ample effect. Some physicians utilize oxytocics of this kind during the first and second stages of labor in the mistaken notion that delivery is thereby hastened. This practice is a possible source of danger to both mother and fetus. During the third stage of labor, these drugs should not be used until at least after presentation of the head, and preferably after passage of the placenta. Ordinarily 0.2 mg. of ergonovine is injected intraven-

ously at this stage to bring about prompt and sustained contraction of the uterus. The effect lasts about 5 hours and prevents excess blood loss. It also lowers the incidence of uterine infection. A continued effect may be obtained by further administration of the alkaloid, either orally or parenterally.

The average dose is (intravenous or intramuscular) 0.2 mg. and (oral) 0.5 mg.

Ergotamine Tartrate U.S.P. (Gynergen). Ergotamine, one of the insoluble ergot alkaloids, is obtained from the crude drug by the usual isolation methods (q.v.).

The free base occurs as colorless needles or prisms or as a white, crystalline powder. It is only slightly soluble in water, but is soluble in alcohol and in the immiscible solvents. It acts as a mono-acidic base and forms crystalline salts. Among these, the tartrate $(C_{33}H_{35}O_5N_5)_2 \cdot C_4H_6O_6$, is official, occurring in the form of white crystals. The crystals are not very soluble in water (1:500) or alcohol (1:500), but are soluble enough to permit the preparation of solutions of adequate strength.

Previous to the discovery of ergonovine, ergotamine was the ergot drug of choice as a uterine stimulant either orally or parenterally. Because it offered no advantage over ergonovine except for a more sustained action and, in addition, was more toxic, it fell into disuse. However, it has been employed for a new use, i.e., in the treatment of migraine headache, in which capacity it is reasonably effective. It is of no value in other types of headache and sometimes fails to abort migraine headaches. It has no prophylactic value. It is customary to administer 0.25 mg. subcutaneously to determine whether idiosyncrasy to the drug exists. In the event that no sensitivity is shown, the full dose of 0.5 mg. is injected. Oral or sublingual administration may be resorted to, but they are much less effective than the parenteral route. Care should be exercised in its continued use to prevent signs of ergotism. More recently, a closely related derivative, dihydroergotamine (q.v.), has been proposed

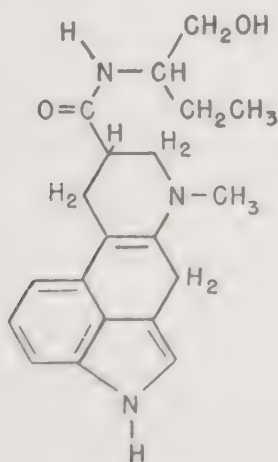
as a more efficient replacement for ergotamine for migraine headache.

The average dose is 0.5 mg. intramuscularly and 1 mg. orally.

Dihydroergotamine (D.H.E.45). This compound is produced by the hydrogenation of the easily reducible double bond in the lysergic acid portion of the ergotamine molecule. The compound is marketed only in ampule form as dihydroergotamine methanesulfonate.

Dihydroergotamine, although very closely related to ergotamine, differs significantly from the latter in its action. For all practical purposes, the uterine action is lacking. However, the sympatholytic action is stronger. Nausea and vomiting are at a minimum, as is its cardiovascular action. One of its principal uses has been in the relief of migraine headache in a manner similar to ergotamine, over which it excels not only in decreased toxicity but also in a higher percentage of favorable results. According to authorities, good results are obtainable in about 75 per cent of the cases treated. Because the drug is not very effective orally, it usually is administered subcutaneously, intravenously or intramuscularly in a dose of 1 or 2 cc. (1 or 2 mg.) which may be repeated in an hour if necessary.

Methergine. Methergine is a synthetic derivative of lysergic acid and marks the first time that a synthetic member of this group has been prepared. It is *d*-lysergic acid-*dl*-



Methergine

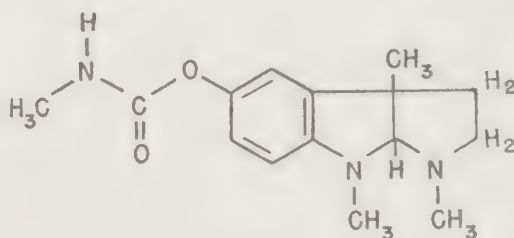
hydroxybutylamide-2 and is prepared by the method of Hofmann and Stoll.⁴⁵ Isolysergic acid azide is condensed with *d*-2-amino-*l*-butanol, and the resultant product is subjected to a transposition treatment to obtain the product.

The drug is very similar to ergonovine in its pharmacologic actions. It is, however, about one and one-half to two times as powerful as ergonovine in its action. The action of methergine is quicker and more prolonged than that of ergonovine. It has been shown that it is relatively nontoxic in the doses used. It is used for the same conditions as ergonovine, and the usual dose is 0.2 mg. in the form of an ampule solution (1 cc.). It is also marketed for oral use in 0.25 mg. tablets to be used in a dose of one tablet two to four times daily.

CALABAR BEAN AND ITS ALKALOIDS

Calabar bean consists of the dried ripe seed of *Physostigma venenosum* and was formerly official in the U.S.P. IX. The crude drug is quite poisonous. In West Africa the bean is known as the "ordeal bean" in allusion to the native usage of the bean as an ordeal for accused persons. Unless vomiting occurred, the drug usually proved fatal, guilty or not guilty. The toxicity is attributed to the alkaloids which are present to the extent of 0.15 to 0.3 per cent. The chief alkaloids are physostigmine and genseserine (an amine oxide of physostigmine).

Physostigmine (Eserine). This alkaloid



Physostigmine

was first isolated from Calabar bean by Jobst and Hesse (1864) and named *physostigmine*. In the following year, it was isolated by Vee

and Leven who named it *eserine*. Although it became apparent that the two were identical, both names have persisted in use.

Physostigmine may be prepared from the crude drug in the usual manner (q.v.).

The free base is levorotatory and exists in a crystalline state in two forms (m.p. 86-7° C. and m.p. 105-6° C.). The higher melting form is the more stable. The crystals are white but tend to slowly turn red on exposure to air and light. The redness is due to the formation of an oxidation product known as *rubreserine*. The formation of rubreserine occurs more rapidly in solutions of the alkaloid upon addition of alkali such as sodium or potassium hydroxide. It is only slightly soluble in water, but it is readily soluble in alcohol, the immiscible solvents or fixed oils.

It behaves as a mono-acidic base and readily forms salts such as the hydrohalides, sulfate and salicylate. Salt formation takes place at the nitrogen which is farthest removed from the aromatic nucleus since this amino nitrogen is more aliphatic in character than the one adjacent to the benzene ring. The sulfate and salicylate are the commonly used salts, but the salicylate is more generally accepted, in spite of a lesser solubility, because it is not deliquescent as is the sulfate.

The structure of the alkaloid was elucidated by the work of many researchers, although the true structure was finally postulated by Stedman and Barger.⁴⁶ Total synthesis was effected by the American workers, Julian and Pikel.⁴⁷

Physostigmine Salicylate (Eserine Salicylate) U.S.P. $C_{15}H_{21}N_3O_2 \cdot HC_7H_5O_3$, may be prepared by neutralizing an ethereal solution of the alkaloid with an ethereal solution of salicylic acid. Excess salicylic acid is removed from the precipitated product by washing it with ether.

It occurs "as white or faintly yellow, shining, odorless crystals." Upon prolonged exposure to air and light, the crystals turn red in color. The red color may be removed by

washing the crystals with alcohol, although this causes loss of the compound as well.

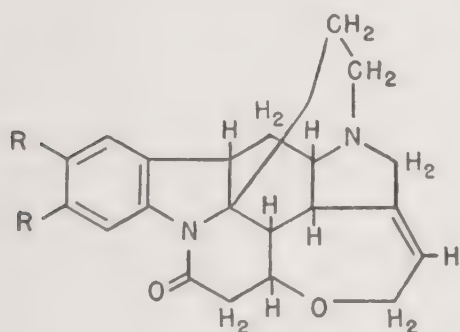
Physostigmine salicylate is soluble in water (1:75), alcohol (1:16) or chloroform (1:6), but is much less soluble in ether (1:250). Aqueous solutions are slightly acidic in reaction and take on a red coloration after a period of time. The coloration may be taken as an index of the loss of activity of physostigmine solutions. To guard against decomposed solutions, only enough should be made at one time for about a week's use. If it is necessary to sterilize the solution, it can be done by bacteriologic filtration. Physostigmine salicylate solutions are incompatible with the usual alkaloidal reagents, with alkalies and with iron salts.

The main physiologic action of physostigmine results from its ability to inhibit the hydrolysis (by choline esterase) of liberated acetylcholine in the body. This permits the acetylcholine (q.v.) to exert a powerful *stimulation of the parasympathetic nervous system*, which normally does not take place because of continuous acetylcholine hydrolysis. The *ophthalmic effect* (miotic) is due to contraction of the ciliary body. This promotes drainage through the canal of Schlemm and thereby decreases intra-ocular pressure. For this reason, physostigmine is used in the treatment of glaucoma by direct instillation of a 0.1 to 1 per cent solution in the eye. It is directly antagonistic to atropine in the eye and is sometimes used to help restore the pupil to normal size following atropine dilatation. Physostigmine also causes *stimulation of the intestinal musculature*, and because of this, is used in conditions of depressed intestinal motility. In gaseous distention of the bowel, due to a number of causes, physostigmine often aids in the evacuation of gas as well as restoring normal bowel movement. It is administered by injection for this purpose. Much research has been done to find synthetic drugs with a physostigminelike action. This has resulted in compounds of the neostigmine type (q.v.), which, at least for intestinal

stimulation, are superior to physostigmine. The average dose is 2 mg.

NUX VOMICA AND THE NUX VOMICA ALKALOIDS

Nux vomica is the ripe, dried seed of *Strychnos Nux-vomica* and is commonly referred to as "dog buttons." It has long been used as a circulatory and respiratory stimulant, although its principal use today is as a bitter tonic. The crude drug is quite potent and owes its activity chiefly to its alkaloidal content. Its principal alkaloids are strychnine and brucine, each occurring to the extent of about 1 to 1.4 per cent. The official N.F. requirement is 1.15 per cent of strychnine. The following probable formulae show the close relationship between the two alkaloids.



Strychnine, R = H
Brucine, R = OCH₃

Strychnine N.F. This alkaloid was first isolated by Pelletier and Caventou in 1817. It is prepared from powdered nux vomica by adaptations of the usual extraction methods, the principal difficulty lying in the separation of brucine from the strychnine.

It occurs as colorless crystals or as a white crystalline powder. It is odorless, has a bitter taste and is stable. The alkaloid is not very soluble in water (1:6,420, 1:3,100 at b.p.), but is more soluble in alcohol (1:136, 1:34 at b.p.). It is quite soluble in chloroform (1:5), but surprisingly it is only very slightly soluble in ether.

Strychnine is a mono-acidic base, although it contains two nitrogen atoms. The nitro-

gen involved in salt formation is the one farthest removed from the aromatic benzene ring. The other nitrogen, being an amide nitrogen, has no basic properties. It forms salts readily, the sulfate, nitrate and phosphate being used therapeutically. Table 50 (page 464) summarizes some of the pertinent information with regard to strychnine, brucine and their official salts.

Strychnine has had an irregular career in therapeutics. In the medical practice of an earlier day it had a reputation as a cardiovascular stimulant, respiratory stimulant and bitter tonic. Although strychnine is a central nervous system stimulant, present-day opinion holds that the therapeutically desirable effects are obtainable only with doses bordering on the toxic. As a bitter tonic, the only effect obtained with the alkaloid is bitterness, because the desired stimulation of intestinal musculature is not obtained with therapeutic doses. For this reason, also, the inclusion of strychnine in various cathartic pills and preparations is without basis. According to Goodman and Gilman, the principal therapeutic value of strychnine resides in its use for the treatment of poisoning by central nervous system depressants, e.g., barbiturates.

Perhaps one of the most important features of strychnine is its toxicity. It causes, in large doses, an exaggerated reflex response to external stimuli. In sufficiently large doses the victim goes into tetanic convulsions involving all muscles symmetrically. Death results from respiratory arrest due to involvement of the diaphragm.

The average dose is 1.5 mg.

Brucine Sulfate N.F. This alkaloid was isolated from nux vomica by Pelletier and Caventou in 1819. The base may be obtained as a by-product during the manufacture of strychnine. Its properties and those of its principal salt, the sulfate, are tabulated in Table 50 (page 464).

Brucine is said to possess only one-sixth the toxicity of strychnine, and it possesses a much weaker, but similar, physiologic

TABLE 50. PROPERTIES OF STRYCHNINE AND BRUCINE AND THEIR SALTS

COMPOUND	DESCRIPTION	AVERAGE DOSE	WATER	ALCOHOL	SOLUBILITY* GLYCERIN	CHLOROFORM	ETHER
Strychnine N.F. $C_{21}H_{22}O_2N_2$	Colorless, transparent, prismatic crystals or a white crystalline powder. Odorless, bitter and stable.	1.5 mg.	6,420 3,100 at b.p.	136 34 at b.p.		5	Very slightly
Strychnine Nitrate N.F. $B \cdot HNO_3^\dagger$	Colorless, glistening needles or a white crystalline powder. Odorless, bitter and stable.	2 mg.	45 10 at b.p.	150 80 at 60° C.	50	105	Insol.
Strychnine Phosphate N.F. $B \cdot H_3PO_4 \cdot 2H_2O$	White crystals or a white powder. Odorless, bitter and stable.	2 mg.	30 more sol. in hot water.	Slightly			
Strychnine Sulfate U.S.P. $B_2 \cdot H_2SO_4 \cdot 5H_2O$	Colorless' or white crystals or white crystalline powder. Odorless, efflorescent.	2 mg.	35 7 at b.p.	85 25 at 70° C.	Freely	220	Insol.
Brucine $C_{23}H_{26}O_4N_2 \cdot 4H_2O$	White crystals or a white crystalline powder. Odorless and bitter.	approx. 2 mg.	320 150 at b.p.	1.3	36	5	187
Brucine Sulfate N.F. $B_2 \cdot H_2SO_4 \cdot 7H_2O$	Small, white crystals or powder. Sensitive to light.	2 mg.	70 more sol. at b.p.	Sparingly (approx. 105)		170	

* The numbers given in the solubility table indicate the number of cc. of solvent required to dissolve 1 Gm. of the compound at 25° C., unless otherwise specified.
† The letter "B" represents the respective alkaloidal base, e.g., B in the case of strychnine is $C_{21}H_{22}O_2N_2$.

action. The principal therapeutic value of brucine seems to lie in its bitter taste, a property which is made use of in stimulating salivary and gastric secretions. Brucine and preparations containing it are probably of the greatest interest to veterinarians as tonics. Brucine is said to be the most bitter substance known (about 12 times as bitter as quinine and about 4 times as bitter as strychnine). Because of this extreme bitterness, it is used for denaturing alcohol and inedible fats.

The average dose is 2 mg.

OFFICIAL OCCURRENCE N.F.	STRYCHNINE
Aloin, Strychnine and Belladonna Pills	1.0 mg. pill
Aloin, Strychnine, Bel- ladonna and Cascara Pills	0.5 mg. pill
Aloin, Strychnine, Bel- ladonna and Ipecac Pills	1.0 mg. pill
Compound Hypophos- phites Syrup	0.01 per cent
OFFICIAL OCCURRENCE N.F.	PER CENT STRYCHNINE SULFATE
Iron, Quinine and Strychnine Elixir . . .	0.0175
Nux Vomica Alkaloids Solution	1.6
OFFICIAL OCCURRENCE N.F.	PER CENT STRYCHNINE NITRATE
Compound Glycero- phosphates Elixir . . .	0.0125
OFFICIAL OCCURRENCE N.F.	PER CENT STRYCHNINE PHOSPHATE
Iron, Quinine and Strychnine Phos- phates Elixir	0.025
OFFICIAL OCCURRENCE N.F.	PER CENT BRUCINE SULFATE
Nux Vomica Alkaloids Solution	1.6

GLYOXALINE GROUP

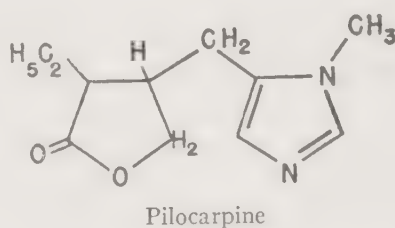
This group also could be termed the "imidazole group," and indeed, is often so designated. The name "glyoxaline" is synonymous with "imidazole" and was originally derived from the fact that the latter

was first prepared by the interaction of glyoxal and ammonia.

PILOCARPUS AND THE PILOCARPUS ALKALOIDS

Pilocarpus (*Jaborandi*) was formerly official in the U.S.P. IX and was defined as the leaflets of *Pilocarpus Jaborandi* or *P. microphyllus*. The drug was first used in medicine by Coutinho, a Brazilian physician, in 1874. Later investigations showed that the effects were of a parasympathomimetic nature. Its activity subsequently was shown to be due to its alkaloidal content. The drug contains about 1 per cent of total alkaloids, among which are pilocarpine, pilocarpidine, isopilocarpine and others. Chief among these is pilocarpine, which occurs to the extent of about 0.5 per cent in *Pilocarpus*, and to this alkaloid may be assigned the principal activity of the drug.

Pilocarpine. This base was first isolated from pilocarpus by Hardy (1875), characterized mainly by Jowett and Pinner and first synthesized by Preobrashenski and co-workers in 1933. The alkaloid was first recognized by the U.S.P. VIII.



It usually occurs as a colorless, viscid liquid, but has been crystallized. It behaves as a mono-acidic base, forming well-crystallized salts. The most important of these are the hydrochloride and the nitrate. Although the hydrochloride possesses a solubility advantage over the nitrate, the latter is considered by many to be more desirable because of its nondeliquescent nature. Inspection of the pilocarpine structure reveals that it is a lactone (of pilocarpic acid) and, for this reason, it is soluble in alkalies through formation of a sodium salt.

Pilocarpine has a physostigminelike action, but appears to act by direct cell stim-

ulation rather than by disturbance of the choline esterase-acetylcholine relationship as is the case with physostigmine. Its outstanding pharmacologic effects are the production of copious sweating, salivation and gastric secretion. At one time it was used as a sudorific in cases of dropsy to aid in the elimination of excess fluid, but this use has become almost obsolete. It also exerts a miotic effect upon the eye and, because it causes a drop in intraocular pressure, it is used as a 1 to 2 per cent solution (i.e., of the salts) in treating glaucoma. Secretion in the respiratory tract is noted following therapeutic doses, and the drug is, therefore, sometimes used as an expectorant. Its occurrence in hair restorers is based on a supposed stimulant action on the sebaceous glands, but it is probably of little value in this capacity.

Pilocarpine Hydrochloride N.F. This salt, $C_{11}H_{16}O_2N_2 \cdot HCl$, occurs "as colorless, translucent, odorless, faintly bitter crystals." It is light-sensitive and is hygroscopic. The hydrochloride is very soluble in water (1:0.3) and in alcohol (1:3, 1:1.5 at 60° C.), but is less soluble in chloroform and in ether. Aqueous solutions are acid in reaction and may be sterilized by autoclaving.

Its uses are the same as those of pilocarpine (q.v.).

The average dose is 5 mg.

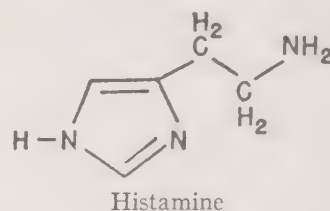
Pilocarpine Nitrate U.S.P. This salt, $C_{11}H_{16}N_2O_2 \cdot HNO_3$, occurs "as shining white crystals" which are not hygroscopic but are light-sensitive. It is soluble in water (1:4), less soluble in alcohol and insoluble in chloroform and in ether. Aqueous solutions are slightly acid to litmus and may be sterilized in the autoclave. The alkaloid is incompatible with alkalis, iodides, silver nitrate and the usual alkaloidal precipitants.

Its uses are the same as those of pilocarpine (q.v.).

The average dose is 5 mg.

Histamine. This alkaloid was first obtained from ergot by Barger and Dale in 1910. Since then it has been found to be of

wide occurrence in both plant and animal tissue. It may be obtained from putrefied meat products.



Histamine occurs as white crystals which are soluble in water but only slightly soluble in alcohol. It is basic and forms salts of which the phosphate and hydrochloride are used medicinally.

Histamine possesses numerous pharmacologic actions. In fact, the multiplicity of actions is a serious drawback to its therapeutic use and, consequently, it is not used extensively. One of the first effects observed was its stimulating action on the uterus. However, because of undesirable side-effects, it is not used for this purpose. It readily causes gastric secretion, particularly of hydrochloric acid, and finds an application in gastric function tests to distinguish between false and true achlorhydria. For this use the official histamine phosphate solution is used. Histamine causes a sharp drop in blood pressure due to a relaxing effect on capillary walls. The increased circulation thus effected is the basis of its use by local application, i.e., by inunction, iontophoresis or subcutaneously in the relief of muscular pain, neuralgias and rheumatoid arthritis. Histamine has also been used with success in the treatment of Meniere's disease because histamine affects capillary permeability. Sheldon and Horton⁴⁸ have postulated that the disease originates in the inner ear and results from local alteration of the capillary wall permeability.

Other uses of histamine are for histamine headache (erythrocephalgia), in testing the integrity of the peripheral nerves and to test the efficiency of the peripheral circulation.

The role of histamine in allergic disorders is discussed elsewhere in this text; it has

given rise to a new group of drugs termed the antihistaminics (q.v.).

Histamine Phosphate (Histamine Acid Phosphate) U.S.P., $C_5H_9N_3 \cdot 2H_3PO_4$, occurs "as colorless, odorless, long prismatic crystals" which are stable in air, but light-sensitive. The salt is water-soluble (1:4) and gives solutions which are acid to litmus. Solutions may be sterilized by autoclaving. A solution containing 1 Gm. in each 1,000 cc. is official as *Histamine Phosphate Injection*.

The uses of histamine phosphate or of the official solution are the same as those cited for histamine.

The average dose is 0.3 mg.

ALKALOIDAL AMINES

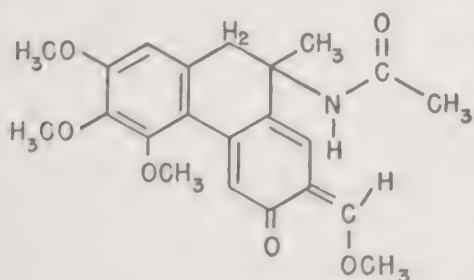
EPHEDRA AND EPHEDRINE

See Chapter 14.

COLCHICUM AND ITS ALKALOIDS

The dried seeds and corm of *Colchicum autumnale* (autumn crocus or meadow saffron) are official in the N.F. Galenical preparations of these drugs have been used in the treatment of gout since the sixteenth century. The activity of colchicum and its preparations is due to the alkaloids which it contains, chiefly colchicine. The seeds and corm, respectively, are required to contain a minimum of 0.45 and 0.35 per cent of colchicine.

Colchicine U.S.P. This alkaloid was first isolated from colchicum by Pelletier and Caventou in 1819. It may be prepared commercially from the crude drug by extraction with alcohol and subsequent purification of the extract.



Colchicine

It is odorless and occurs as "pale yellow, amorphous scales, or powder." This levorotatory base is light-sensitive. It is soluble in water (1:25), freely soluble in alcohol and in chloroform, but somewhat less soluble in ether (1:220). Aqueous solutions are neutral and may be sterilized by the intermittent method or by passing through a bacteriologic filter.

Colchicine, when crystallized from chloroform, takes up chloroform of crystallization. For this reason, the U.S.P. sets up a test for chloroform to insure its absence in the official compound. Colchicine, being an amide, is only faintly basic and does not form stable salts.

Colchicine is used in therapeutics only for its favorable effect on acute attacks of gout. The mechanism of action is not understood, but it is clear that it does not increase uric acid elimination. Administration of the alkaloid is usually oral and should be instituted as early in the attack as possible. It is without value in chronic cases. Because the drug is extremely poisonous, its use should not be continued after the pain accompanying the attack has been alleviated.

An interesting effect of colchicine is its ability to arrest mitosis in the metaphase, i.e., the stage of cell division when the chromosomes line up at the equator of the cell. Because it causes duplication of the chromosomes, i.e., heteroploidy, it has been used experimentally to produce large flowers, giant fowl, etc.

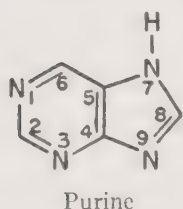
The average dose is 0.5 mg.

OFFICIAL OCCURRENCE	PER CENT COLCHICINE
N.F.	
Sodium Salicylate and Iodide with Colchicine Ampuls	Variable

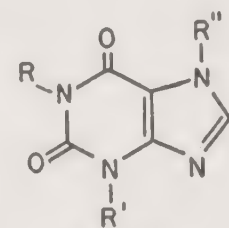
PURINE GROUP

The members of this group are all related to the parent substance, purine. Compounds with purine type structure occur widely distributed among natural products, e.g., in uric acid, coffee, tea, cocoa, nucleic acids, enzymes, etc. In medicine, the most valuable purines, or more specifically *xanthine* deriva-

tives, are caffeine, theobromine and theophylline. The worldwide use of stimulating drinks containing one or more of these principles causes them to assume added significance.



Purine

Xanthine
(R, R' & R'' = H)

The following table summarizes the structural relationships of these alkaloids, utilizing the xanthine formula given above as its basis.

COMPOUND	R	R'	R''	COMMON SOURCE
Caffeine	CH ₃	CH ₃	CH ₃	Coffee, tea
Theophylline	CH ₃	CH ₃	H	Tea
Theobromine	H	CH ₃	CH ₃	Cocoa

Although numerous syntheses of purines have been effected, that of Traube⁴⁹ (1900) is perhaps the most satisfactory. To synthesize uric acid, cyanoacetic acid and urea are used as starting materials, forming cyanoacetylurea (I), which immediately changes to 4-imino-2,6-dioxyhexahydropyrimidine (II) on treatment with 40 per cent sodium hydroxide. This product is converted, with nitrous acid, to iminoviolic acid (III), which, upon reduction with zinc and sulfuric acid, yields 4,5-diamino-2,6-dioxypyrimidine (IV). Condensation of the diamine with ethylchlorocarbonate gives a urethane derivative (V). The sodium salt of the urethane, when heated, is transformed to uric acid (VI). (See the equations at the top of page 469.)

The individual xanthine derivatives, e.g., caffeine, theophylline, etc., may be synthesized by the Traube method with modifications (q.v.).

The relative pharmacologic potencies of the xanthines are summarized by Goodman and Gilman⁵⁰ in Table 51 (page 469).

In therapeutics, caffeine is the drug of choice among the three xanthines for obtaining a *stimulating effect* on the *central nervous system*. This stimulant action is almost physiologic in nature and helps to combat fatigue and sleepiness. Apparently, little tolerance is built up toward caffeine stimulation and, therefore, habitual coffee drinkers continue to experience stimulation from day to day. The amount of caffeine in an average cup of coffee or tea is from 100 to 150 mg., and it is obvious that a cup or two of the beverages represents very nearly a therapeutic dose of caffeine. Ordinarily, caffeine is not of value in other conditions, in spite of its other pharmacologic actions, because of the possibility of causing restlessness, insomnia, etc. Although Table 51 shows that theophylline exceeds theobromine in *diuretic activity*, the latter is said to be preferable because of fewer side reactions (gastric and renal irritation) and a more persistent action. Tolerance to the diuretic effect is noted with the xanthines. It might be added that all of the xanthines have been used less as diuretics since the advent of the more potent mercurials. Recently, however, theophylline has been used with the mercurials (e.g., Mersalyl and Theophylline Injection) because the combination seems to be more effective than the latter alone. For *cardiac* and *coronary effects*, theophylline is the most widely used of the xanthines, especially in the form of aminophylline (theophylline ethylenediamine). Aminophylline is also preferred as a *relaxant* of the smooth muscle in the *bronchi*. Use of the xanthines by gouty individuals is not contraindicated since they break down in the body to urea and not to uric acid.

Caffeine U.S.P. (Theine). Caffeine was first isolated by Runge in 1820, and was later synthesized by a variety of methods. Commercially, the principal source of caffeine in the United States is said to be from theo-

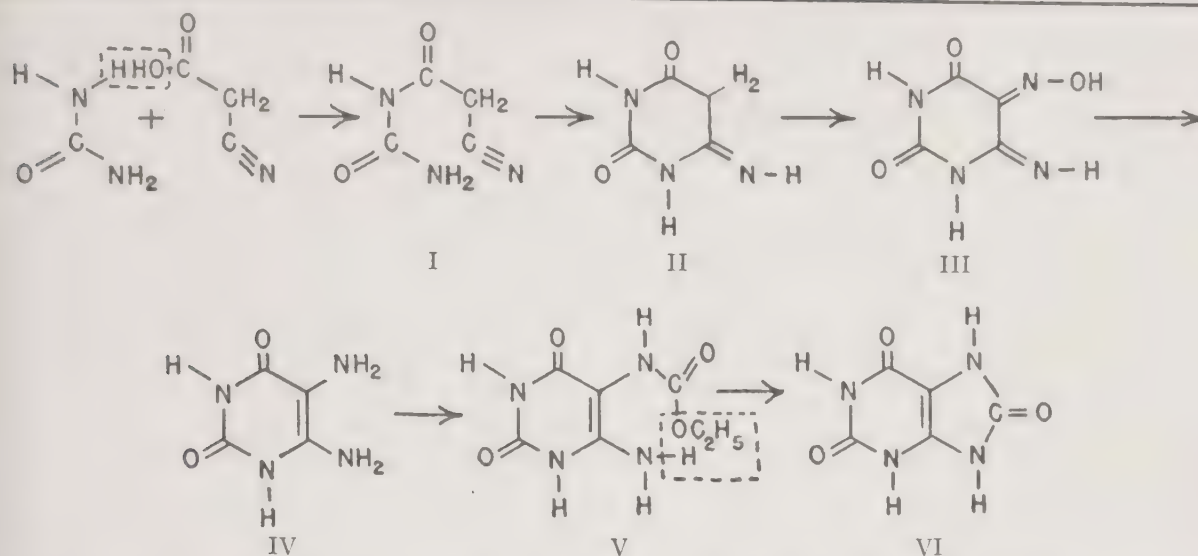


TABLE 51. RELATIVE PHARMACOLOGIC POTENCIES OF THE XANTHINES*

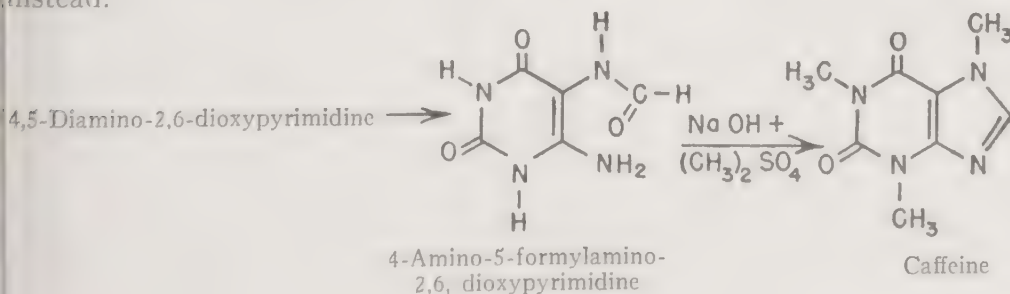
XANTHINE	C.N.S. STIMULATION	RESPIRATORY STIMULATION	DIURESIS	CORONARY DILATATION	CARDIAC STIMULATION	SKELETAL MUSCLE STIMULATION
Caffeine	1†	1	3	3	3	2
Theophylline	2	2	1	1	1	3
Theobromine	3	3	2	2	2	1

* From Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, Macmillan, 1941, p. 275.

† 1 = most potent.

bromine, through a process of methylation.⁵¹ Totally synthetic caffeine has not been an important factor because it costs more than the partially synthesized variety. Insofar as caffeine from natural sources is concerned, that from tea wastes is by far more important than that obtained by the decaffeination of coffee. A recent synthesis of caffeine together with references to the literature of the subject has been published.⁵² This synthesis is essentially the Traube synthesis of uric acid (q.v.) with the difference entering in the conversion of 4,5-diamino-2,6-dioxypyrimidine (IV) (see page 469) to caffeine instead.

Caffeine "occurs as a white powder, or as white, glistening needles, usually matted together." The alkaloid is odorless and possesses a bitter taste. It is soluble in water (1:50), alcohol (1:75), or chloroform (1:6), but is not so soluble in ether. Its solubility is increased in hot water (1:6 at 80° C.) or alcohol (1:25 at 60° C.). Aqueous solutions are neutral to litmus. Crystallization of the base from water gives a compound with one molecule of water of crystallization, whereas use of the other solvents gives an anhydrous compound. The hydrated compound is efflorescent.



Caffeine is a very weak base and does not readily form salts. Its salts are unstable in aqueous or alcoholic solutions, decomposing into the free base and the acid. The official *Citrated Caffeine* is not a true salt of caffeine, being merely a mixture of equal parts of citric acid and caffeine. This mixture is more soluble in water (1:4) than the caffeine alone. Other mixtures which are official are *Caffeine and Sodium Salicylate* and *Caffeine and Sodium Benzoate*, each containing equal parts of the components. They are used to solubilize the caffeine and the latter is of particular use for intramuscular injection.

Recent studies⁵³ have shown that there is no difference in the pharmacologic response to caffeine derived from synthetic or natural sources. Caffeine, as previously mentioned, is used as a central nervous system stimulant for a variety of conditions. It may be used to provide a mild stimulation, in this way facilitating and increasing the total amount of work done. It appears to affect the portion of the brain that has to do with sensory perceptions, making for a better and clearer flow of thought. In larger doses it is used to combat central depression caused by such drugs as morphine, barbiturates, etc.

The average dose is 0.2 Gm.

OFFICIAL OCCURRENCE	PER CENT CAFFEINE
U.S.P.	
Caffeine and Sodium Benzoate.....	50.0
Citrated Caffeine	50.0
N.F.	
Caffeine and Sodium Salicylate.....	50.0

Theobromine. This alkaloid, $C_7H_8O_2N_4$, is usually a by-product of cocoa and chocolate manufacture, being obtained by extraction from cocoa shells and cocoa cake. It may also be synthesized.

Theobromine occurs as an odorless, white, crystalline powder with a somewhat bitter taste. It is not very soluble in water (1:1,000, 1:115 at b.p.) or alcohol (1:1,400, 1:260 at b.p.). It may be made much more soluble, however, by mixing it, as its sodium salt, in molecular proportions with sodium ace-

tate to form *Theobromine and Sodium Acetate* (U.S.P.), or with sodium salicylate to form the N.F. *Theobromine and Sodium Salicylate* (Diuretin, Theobromine-Sodio-Salicylate). These are soluble in water to the extent of 1:1.5 and 1:1, respectively. Another preparation on the market is Theobromine Calcium Salicylate (Theocalcin, Calcium Diuretin, Theosol). Mixtures containing the sodium derivative, when dissolved in water, impart a decidedly alkaline reaction to the solution (approx. pH=10).

The chief use of theobromine is as a diuretic in the treatment of various types of edemas. Because of its insolubility, it is used mostly in the form of the double salts which, as indicated, are much more soluble and cause less gastric irritation than the free base.

The average doses are as follows: Theobromine and Sodium Acetate, 0.5 Gm.; Theobromine and Sodium Salicylate, 1 Gm.

OFFICIAL OCCURRENCE	PER CENT THEOBROMINE
U.S.P.	
Theobromine and Sodium Acetate	55-65
N.F.	
Theobromine and Sodium Salicylate	46.5

Theophylline U.S.P. Theophylline, $C_7H_8N_4O_2 \cdot H_2O$, occurs in tea leaves. However, the amount is too small to be of commercial importance, and, consequently, most of it is made synthetically. A common synthesis is from dimethyl urea and cyanoacetic acid according to the Traube method. A recent paper⁵² indicates that methylation of 4-imino-2,6-dioxyhexahydropyrimidine (see compound II, page 469) is successful, forming the 1,3-dimethyl derivative. Subsequent steps are essentially the same as those for the synthesis of caffeine (q.v.), with the exception that the final methylation is omitted.

This alkaloid occurs as an odorless, bitter, white, crystalline powder which is stable in air. It is somewhat soluble in water (1:120) and in alcohol (1:80), but is sparingly soluble in ether and chloroform. Theophylline

is soluble in solutions of the alkali hydroxides by a mechanism which is not fully understood. As will be noted, the two methyl groups of theophylline are in the 1 and 3 positions, which precludes the type of enolization which takes place in theobromine and barbituric acid derivatives. Whatever the manner in which the sodium derivative of theophylline forms, it does not appear to be due to the conventional enolization procedure. Double salts of sodium theophylline with other salts are similar to those encountered with theobromine. The only official combinations are Theophylline and Sodium Acetate U.S.P. and Aminophylline (Theophylline Ethylenediamine) U.S.P. The former is an equimolecular mixture of sodium theophylline and sodium acetate, whereas the latter is a mixture containing two molecules of theophylline with one molecule of ethylenediamine and corresponds to the formula



These preparations are more soluble in water than theophylline, Theophylline and Sodium Acetate being soluble 1:25 and Aminophylline 1:5. The aqueous solutions are quite alkaline in reaction and gradually absorb carbon dioxide from the atmosphere, liberating free theophylline.

Theophylline is used as a myocardial stimulant and as a diuretic. In the form of its combinations it is also used as a coronary dilator. In this respect, the most important compound is aminophylline. According to the N.N.R. (1947), the use of xanthines in coronary artery disease has not been sufficiently well-evaluated clinically to warrant acceptance of the claims made for it. Aminophylline is also used for its bronchial relaxing effect in cases of bronchial asthma, particularly in patients who are not relieved by epinephrine. Aminophylline is obtainable as a powder, tablets, ampules and suppositories.

Average dose: Theophylline—0.2 Gm.; Theophylline and Sodium Acetate—0.2 Gm.;

Aminophylline—0.2 Gm. (oral), 0.25 Gm. (intramuscular or intravenous).

OFFICIAL OCCURRENCE U.S.P.	PER CENT THEOPHYLLINE
Aminophylline	75-82
Mersalyl and Theophylline Injection	33
Theophylline and Sodium Acetate	55-65

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27

Antibiotics

PENICILLIN
STREPTOMYCIN
TYROTHRIN
BACITRACIN

AEROSPORIN
CHLOROMYCETIN
AUREOMYCIN
OTHER COMPOUNDS

The term antibiotic was coined in 1942 in a sense quite restricted from the generic one. Theoretically, it might describe any substance that is inimical to life of any kind, since it comes from the Greek *anti* meaning against and *bios* meaning life or mode of life. Thus, the word could include any substance that is poisonous to animals or vegetables. However, quite early biologists had adopted "antibiosis" as a term for an antagonism between organisms to the detriment of one of them, and when penicillin and its allies were discovered, it was quite natural to call them antibiotics. Although in recent years substances have been isolated from animals and higher plants that have antagonistic actions toward micro-organisms, yet it would seem logical to restrict the definition to include only products from the lower plants, such as bacteria and fungi. Otherwise, the term would become of little significance; if we admit substances from higher plants and from animals, such as volatile oils and antibodies, then we also must include the hundreds of synthetic poisons. In any event, it appears to be the

consensus that the word antibiotic should be restricted to those substances, produced by certain lower, vegetable organisms, that are inimical to the existence and growth of other micro-organisms, especially those that produce disease in man and other animals.

The subject has but recently become prominent, in spite of the fact that the underlying basis has been known for nearly seventy-five years. Indeed, the beginnings of the subject are usually attributed to Pasteur and Joubert in 1877, who made the observation that the products from certain air-borne organisms are inimical to the growth of the anthrax bacillus. The first serious attempt to make use of such a fact was introduced 22 years later, when Emmerich and Loew suggested that pyocyanase from *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), discovered by Bouchard in 1889, could be employed to treat anthrax and diphtheria. In 1922, Fleming discovered the carbohydrate lysozyme, which is somewhat antimicrobial and is present in a variety of animal tissues, and the investigation of this

substance occupied the attention of many for several years. In the meantime, mycophenolic acid (1896), kojic acid (1912) and penicillic acid (1913) had been isolated from the products of growth of certain fungi and found to have antibacterial action. Up to the time of Fleming's accidental discovery of penicillin in 1928, there were also reported pyocyanine (1924), actinomycetin (1924) and violacein (1927). From that time to the epochal work of the Oxford group, first published in 1940, there appeared papers on lactenin (1930), citrinin (1931), puberulic and puberulonic acids (1932), diplococcin (1933), gliotoxin (1936), fumigatin (1938), iodinin (1939), simplexin (1939) and gramicidin (1939). Most of these compounds were not purified at the time and exhibited such a low potency or high toxicity that they were more or less only of academic interest.

The real start in this important field was made by Florey and his associates at Oxford. They decided in 1938 to make a restudy of the whole list of antibiotics with a view to applying some of them in chemotherapy. In due time their attention was directed to penicillin, which had previously been described as very unstable. Clutterbuck, Lovell and Raistrick had attempted the isolation of the substance a few years before, and their work had indicated that penicillin is not as unstable as had been supposed. The findings of Florey and Chain, together with subsequent work by their associates at Oxford, are now well known, and it is not necessary to review here the intense interest that was so engendered and rapidly spread throughout the world. The publication of the first paper in August 1940 started a chain of investigations that has revolutionized the therapy of infectious diseases. The end of this is not yet in sight, in spite of the fact that in 1944 Hoogerheide¹ made the observation: "Although the possibilities for such discovery are limitless, it is by no means certain that this field will prove to be the rich mine for therapeutic agents that many investigators believe it to be."* Since the

date of that statement, we have received streptomycin, bacitracin, actidione, aerosporin, chloromycetin, neomycin and aureomycin, and each new year seems to bring increasing possibilities.

Up to the present writing, thousands of organisms have been cultivated through the efforts of many workers and examined for evidence of antibiotic activity. The discoverer of aureomycin, for example, is said to have isolated 3,400 strains of micro-organisms from soil alone. While most of such investigations have been unproductive, yet since 1877 more than a hundred products were found promising enough to receive a name. Many of these were produced on a laboratory scale in sufficient amounts to permit extensive trials in therapy, although most of these have ultimately been discarded as too toxic or ineffective in practice. However, the few that are manufactured commercially are overwhelming compensation for the immense amount of work that has been expended, since now many infectious diseases really can be controlled for the first time.

The possibilities of synthetic production, not only of the antibiotics that are useful in practice, but also of an unlimited number of similar agents, must not be discounted. While a few of the natural products are proteins and at present it is not possible to synthesize them, yet most of them appear to be comparatively simple molecules and will be made in the laboratory as soon as enough time has elapsed to allow the necessary determination of structure and the elaboration of methods of synthesis. In this connection it must be noted that less than ten years ago the majority of us had never heard of penicillin, yet this and many other antibiotics can now be made artificially. The greatest hope in the future lies in the studies of successful natural compounds, in order to learn more about the structural units that make them work, and in the possibilities of manufacturing literally thousands of com-

*Hoogerheide, J. C.: *Bot. Rev.* 10:599, 1944.

pounds that contain these units. The ultimate prospects of the fight against pathogenic microbes possibly may depend upon the work of the organic chemist.

PENICILLIN

Penicillin² is a name applied to a closely related group of compounds produced by living cultures of various strains of *Penicillium*, chiefly *P. notatum* Westling and the nearly allied *P. chrysogenum* Thom. These compounds are fairly strong acids but, as such, are extremely unstable and not used. The marketed products are the more stable salts, mainly those of sodium, calcium, aluminum or potassium; in ordinary parlance the term "penicillin" means one of these salts or a mixture of them. The chief compounds that have been separated are named in this country F, G, X and K, corresponding with I, II, III and K in England. All of these have the same fundamental structure, differing only by a single group, which is 2-pentenyl ($\text{CH}_3\text{—CH}_2\text{—CH=CH—CH}_2\text{—}$) in F, benzyl ($\text{C}_6\text{H}_5\text{—CH}_2\text{—}$) in G, *p*-hydroxybenzyl ($\text{HO—C}_6\text{H}_4\text{—CH}_2\text{—}$) in X and *n*-heptyl in K. Using R for this group, the sodium salt has the empirical formula $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_4\text{SRNa}$.

The synthesis in 1946 was accomplished by the collaborative efforts of hundreds of chemists, but unfortunately has not entirely substantiated the accepted formula. Among the degradation products were found *d*-penicillamine, which is a dimethylcysteine, and certain oxazolone derivatives. Early in 1944, several laboratories had reported that condensation of these compounds gives antibiotic activity, but only in small amounts, and it remained for work with radioactive isotopes to show that penicillin was actually being produced. The greatest difficulty was to separate this from the reaction mixture. Finally, workers at Cornell University were able to accomplish this by a long, tedious process, involving activation by pyridine and separation of the trimethylammonium salt of benzylpenicillin, which had all of the

physical and antibiotic properties of the same salt of the natural compound. Although the synthesis had been accomplished, it did not prove the structure because the mechanism of reaction is still obscure. However, a compound of the generally accepted formula could have been produced by the compounds used according to the equation shown at the top of page 477.

Any of the commercial salts are white to brown, amorphous powders that are nearly odorless and somewhat hygroscopic. They are not affected by light but are decomposed at temperatures above 25° C. They are readily soluble in water, but the solutions are precipitated by acids and by many salts of the heavy metals. They are also soluble in other solvents, including glycerin and alcohol, but the latter quickly destroys their activity. Penicillin is comparatively unstable under a variety of conditions, including those found in the gastro-intestinal tract. Acids or bases in excess inactivate it rather readily, so solutions must be adjusted to a pH of from 5 to 7. Oxidizing or reducing agents also abolish its activity, as do a large number of reagents and temperatures above 25° C. In addition, it is decomposed by a great number of bacteria and other micro-organisms, and several of these are found in the lower intestines. Several of the enteric organisms produce an enzyme, penicillinase, which is able to inactivate or destroy it on direct contact.

Crystalline salts of penicillin G are also marketed, and especially purified forms are used as quality standards. The commercially prepared articles are not necessarily very pure, because they can be crystallized and yet contain considerable impurities, but they come from nonaqueous solvents and contain very little or no water. In this dry form they are immensely more stable and can be preserved without refrigeration. Solutions made from them, however, decompose even more rapidly than do those of the amorphous varieties unless the pH is

ate, because of the alkalinity, yet it can be used to form the sodium salt if not in such excess. The solution of sodium salt so received must be free of all pyrogens and contaminating bacteria or other poisonous agents, so it is ultimately refiltered through specially designed media.

The last step in the process involves packaging and the removal of water. After assay to determine the volume of solution necessary in each container, the latter receives this amount from an automatic machine and is placed in a freezing compartment and dried in a vacuum to less than 1 per cent of moisture. After capping and sealing, the product is ready for the market, but samples always must be selected from each batch and carefully analyzed.

In the United States the final product must comply with regulations of the Federal Food and Drug Administration. The unit designated is the activity of 0.6 micrograms of the Penicillin Master Standard, a specific lot of penicillin G in the form of its sodium salt. Assays require that the substance be tested side by side with the working standard and that the values be calculated from graphs. The Oxford cup plate method is usually employed, but any of the other proposed processes could be as serviceable. The test organism is generally *Staphylococcus aureus* H (Heatley strain), although others have been used, for example, *Bacillus subtilis*. Penicillin mixtures for oral or parenteral use are limited to a content of not more than 30 per cent of K. Amorphous and crystalline mixtures are required to have a potency of not less than 500 units per milligram or, when comprising at least 90 per cent of X, not less than 350 units. Crystalline preparations designated as from G are required to contain not less than 90 per cent of G; the sodium salt must have a potency of not less than 1,500 units per milligram, the potassium salt 1,435 units. Noncrystalline salts and their preparations are to be refrigerated at not over 15° C., but the crystalline salts

are stable in dry form without refrigeration for up to three years. Solutions can be kept below 15° C. for a maximum of 10 days, but only if buffered to a pH of above 6.0. Any product or preparation must comply with the regulations for sterility, non-toxicity, freedom from pyrogens, moisture, clarity and pH of solutions, packaging and labeling.

The pharmacologic action of penicillin, other than that on invading micro-organisms, is of little practical importance since it is almost entirely negative. No effects have been observed on any normal functions even when the doses were enormous. When it is injected intravenously, the blood level is maintained for but a short time and then falls off abruptly, largely because of excretion by the kidneys and other organs, but also because of partial destruction. After intramuscular or subcutaneous injection, it is absorbed more slowly; the maximum level in the blood is reached in about 30 minutes and is maintained satisfactorily for an hour or two. Administration by insertion into other cavities, for example, those of the thorax or the abdomen, results also in slow absorption and excretion. If given by mouth, it is subject to destruction by hydrochloric acid in the stomach and by inimical organisms in the intestine, and a relatively small portion of the penicillin reaches the blood stream and the urine. Untoward effects after any mode of administration are rarely encountered, although in the early days before precise methods of preparation were employed, the impurities frequently caused chills with or without fever, eosinophilia, headache, cramps, etc. About the only toxic reaction now observed is a delayed and unexplained appearance of urticaria and contact dermatitis. In general, it may be stated that modern penicillin is the safest of any successful chemotherapeutic agent to date.

The activity of penicillin is more or less specific and in the case of a particular organism is not predictable. Of the bacteria

that are affected, most are gram-positive, but a few important ones of this class are not susceptible. Its action toward the gram-negative group is feeble, with several exceptions such as the gonococcal and meningococcal organisms. Furthermore, it is highly effective against certain spirochetes and at least a few rickettsia and viruses. The important pathogens that are affected in vitro and in vivo are:

Neisseria gonorrhoeae
N. intracellularis
Diplococcus lanceolatus
Streptococcus pyogenes
Str. salivarius
Str. micro-aerophilic
Staphylococcus aureus
Staph. albus
Bacillus anthracis
B. subtilis
Rickettsia prowazeki
 Spirochete of relapsing fever
 Spirochete of Weil's disease
Clostridium botulinum
Cl. septicum
Cl. tetani
Cl. welchii (*Cl. perfringens*)
Actinomyces bovis
Corynebacterium diphtheriae
Streptobacillus moniliformis
 (*Actinomyces mauris-ratti*)
Erysipelothrix rhusiopathiae
Hemophilus ducreyi
Spirillum minus
 Virus of psittacosis
 Virus of ornithosis
Treponema pallidum

Notably not affected are the organisms of tuberculosis, whooping cough, malaria, trypanosomiasis, undulant fever, influenza and typhoid and paratyphoid fever, as well as most rickettsiae and viruses.

It is not known by what mechanism penicillin brings about its effects, although an enormous amount of research has been directed toward answering this question. Some authorities have asserted that the

affected organism is killed, and it must be admitted that there may be some evidence that this happens at times. It is generally held, however, that the reproduction of the organisms is prevented by some means, since bacteria in the presence of penicillin seem to grow immensely larger but do not divide and multiply. The reason why this particular molecule does prevent reproduction is still a secret.

Penicillin is different from other bacteriostatic agents in a number of striking ways. In the first place, it seems to have no deleterious effects at all on higher animals; the few untoward reactions that have been observed in humans probably were attributable to impurities in early products. Contrasted with the ordinary antiseptic, which is a general protoplasmic poison, this is indeed an advantage. Its action does not seem to be influenced by the presence of bodily liquids or tissues, while the effect of an antiseptic in general is considerably reduced in this way. Other antibacterials, such as the sulfonamides and various antibiotics, also seem to have no antagonism to action by penicillin; indeed, there is evidence to support the contention that they may even be synergistic. Another unique difference lies in the slowness with which the antibacterial action takes place, usually two to three hours or more after reaching the site of infection. This is important in a local condition, where the drug must remain in contact for a sufficient period, but it is far more so in systemic infections, because one is then confronted with the problem of maintaining an adequate level in the blood in face of the fact that penicillin is normally excreted rather rapidly. Finally, it is, like other antibiotics, quite definitely selective in its action, although fortunately the causative agents of several important diseases are included in the list of those organisms that are inactivated.

Some, if not all, of the organisms that are susceptible to penicillin can acquire a

resistance to it. This has been repeatedly demonstrated *in vitro* by serial transfers on media carrying increased concentrations, a process equivalent to the usual methods of desensitization. While not so much is known about acquired resistance during *in vivo* administration, the evidence that it can exist is indisputable. The cause seems to consist of underdosage over extended periods, and for this reason, many practitioners routinely prescribe immensely larger amounts than seem actually necessary.

The therapeutic indications for treatment with penicillin are too numerous to review in detail here. For those diseases that are caused by organisms that are susceptible to it, the results in many cases are spectacular, but too often it has been employed without proper identification of the cause. In general, the important indications for the use of penicillin may be stated as infections caused by staphylococci, including septicemia, carbuncles, pneumonia and meningitis; pneumococci; gonococci; meningococci; streptococci, including septicemia, endocarditis and pneumonia; anthrax bacilli; the syphilitic organism; and clostridia, including gas gangrene. In infections caused by those organisms that produce toxins, such as diphtheria and tetanus, it is not recommended as the sole remedy because it can have no effect on the toxins that have already been produced, but it can well be combined with antitoxin treatment.

Penicillin may be administered by practically any known route. When given orally, it is partially inactivated by hydrochloric acid and organisms, but it is also uncertainly absorbed, so that this route requires at least five times the parenteral dose. If so given it should be buffered by a suitable antacid, such as sodium citrate or aluminum hydroxide, but not sodium bicarbonate. By injection, which is used in a great majority of cases, it is preferably given intramuscularly, dissolved either in sterile water or in isotonic solution of so-

dium chloride containing 10,000 to 50,000 units per cubic centimeter, and the injections should be repeated at not less than three-hour intervals. When combined in a vehicle of oil and wax to delay absorption, it will exert a much more prolonged effect and if given in concentrations of 300,000 units per cubic centimeter, need not be repeated oftener than once in 12 to 24 hours. The procaine salt of penicillin G will answer the same purpose even more effectively because it is not very soluble; 1 cubic centimeter containing 300,000 units will provide adequate levels in the blood for from 24 to 48 hours. This salt is no more toxic than other preparations, and the injection is said to be practically painless. For still more prolonged effect it may be injected in the form of penicillin S-R, which is a combination of procaine penicillin G with buffered crystalline sodium penicillin G and is intended for the preparation of an aqueous suspension. It contains 300,000 units of the procaine salt and 100,000 units of the sodium salt in each cubic centimeter. Another means of delaying the excretion of penicillin is by the oral administration of staticin caronamide, 1.5 to 4.0 grams every three to four hours, which inhibits temporarily the tubular excretion.

Subcutaneous administration results in somewhat more erratic absorption and is not often recommended. In severe infections the drug can be given by continuous intravenous infusion, employing a solution containing 25 to 50 units per cubic centimeter and administering 5,000 to 10,000 units every hour. For intrathecal or intracisternal injection in the treatment of meningitis, concentrations of 1,000 units per cubic centimeter are used, but the total dose is limited to about 20,000 units. Inhalation of aerosols or nebulae containing 25,000 to 50,000 units per cubic centimeter every three to four hours provide adequate levels in the blood for treating chronic pulmonary infections and sometimes in pneumonia. Soluble tablets are available for the

preparation of these aerosols, for introducing into milk or water for infants and for sublingual administration. Penicillin may be applied topically in powder form, in isotonic solutions of sodium chloride containing 25 units per cubic centimeter or in ointments containing 500 to 1,000 units per gram. The calcium salt is also used in the form of troches for trench mouth and other infections of the mouth and throat, and in dental cones for insertion into cavities after extraction or in the treatment of dry socket. When used locally, the period of application should not exceed five days, because it may cause epidermal sensitivity, and any later renewal should be made cautiously.

The dosage given in each case will depend on various factors, and definite general schedules cannot be established. In serious infections the average parenteral dose is 200,000 to 300,000 units in a 24-hour period; in chronic pyogenic conditions, 40,000 to 80,000 units are given every six hours and in acute gonorrhea, about 30,000 units are employed every three hours. For oil and wax combinations and procaine penicillin G in oil, single doses of 300,000 units once every 24 hours ordinarily will suffice to keep up the level of penicillin in the blood, but twice this every 12 hours may be needed for severe infections. In active primary syphilis, 60,000 units are injected every 2 to 3 hours until a total of about 5,400,000 units have been given, but only as an adjunct to arseno-bismuth therapy. In any program of treatment, it should be remembered that inadequate dosage may lead to developed tolerance and that administration must not be terminated until significant signs of the infection have disappeared.

Penicillin Calcium U.S.P. occurs as a white to brown powder or as granules or scales, sometimes adhering to the container. Its potency is not less than 500 units for each mg., except when it contains not less than 90 per cent of a salt of penicillin X its potency is not less than 350 units for each

mg." When used for preparing an injection in oil and wax, it must have 750 units for each mg. for concentrations of 100,000 to 200,000 units in each cc. and 900 units for each mg. for 300,000 units in each cc. For oral administration in making troches, tablets or dental cones, it need have only 300 units for each mg.

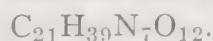
OFFICIAL OCCURRENCE U.S.P.	UNITS OF PENICILLIN CALCIUM
Penicillin Dental Cones	1,000-5,000 units per cone
Penicillin Injection in Oil and Wax..	100,000-300,000 units per cc.
Penicillin Ointment.	
Penicillin Tablets ..	20,000-25,000 units per tablet
Penicillin Troches .	500-20,000 units per troche

Penicillin Sodium U.S.P. occurs as a white to brown powder or as granules or scales, sometimes adhering to the container. "Its potency is not less than 500 units for each mg., except when it contains not less than 90 per cent of a salt of penicillin X its potency is not less than 350 units for each mg." For oral administration in making troches and tablets, it has a potency of not less than 300 units for each mg.

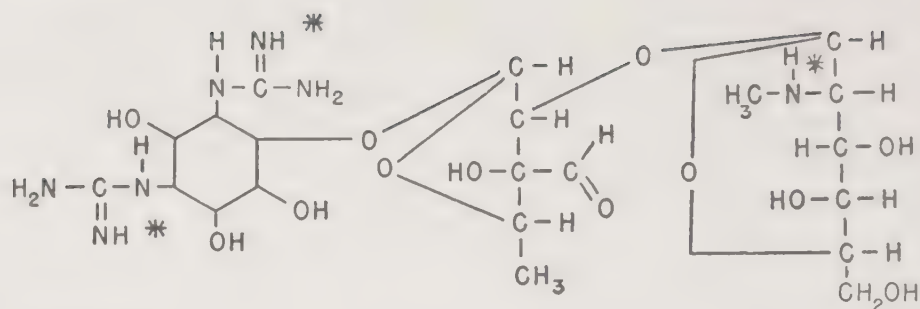
OFFICIAL OCCURRENCE U.S.P.	UNITS OF PENICILLIN SODIUM
Penicillin Tablets ..	20,000-25,000 units per tablet
Penicillin Troches .	500-20,000 units per troche

STREPTOMYCIN

Streptomycin² is a partly purified, active, antibiotic principle produced by certain strains of *Streptomyces griseus* when they are grown on suitable media. It was first isolated by Schatz, Bugie and Waksman in 1944, and has the formula



After considerable research, chemists at Merck & Co. have postulated that the compound is a combination of 1,3-diguanidyl-2,4,5,6-tetrahydroxycyclohexane (streptidene) and a disaccharide streptobiosamine.



* Available for salt formation.

Streptomycin³ is a partly purified, ac-drochloride and as the double salt with calcium chloride ($C_{21}H_{39}N_7O_{12} \cdot 3HCl \cdot CaCl_2$) which is obtained in a higher degree of purity than other salts. These are sterile powders that are soluble in water to give a concentration of from 0.1 to 0.125 gram per cubic centimeter. The salts are stable at room temperature (below 30° C.) for periods up to one year but they are deliquescent and should be kept in the unopened container to prevent contamination and absorption of moisture. Solutions may be stored at room temperature for one week without any loss of potency, but they are most stable if the pH is between 4.5 to 7.0. They cannot be safely heated to sterilize and must, therefore, be prepared and preserved under strict aseptic conditions. The marketed preparations are subject to the regulations of the Food and Drug Administration; they must be sterile, nontoxic and nonpyrogenic, and they must contain no histaminelike compounds and not more than 3 per cent of moisture. The potency is expressed in micrograms of the free base or in units, of which each is equivalent to 1 microgram of the base. The solutions must be free of any turbidity or undissolved material.

The preparation of streptomycin is somewhat like that for penicillin, except that greater stability of the former precludes some of the precautions. After a suitable strain has been cultured to produce maximum activity, the liquid portion is separated by filtration or centrifuging, and the

compound is adsorbed on activated carbon. The carbon is washed with alcohol to remove some impurities, and the streptomycin is eluted by hydrochloric acid and alcohol. After neutralization and filtering, the solution is concentrated by evaporation in vacuum or by precipitation with acetone. The crude material is purified by treatment with phosphotungstic acid, fractionation of the picrate by chromatography and precipitation as the reineckate.

Streptomycin has very little physiologic action in therapeutic doses and gives few toxic reactions in larger ones. It is not absorbed when given by mouth, although it is not significantly destroyed in the gastrointestinal tract. For systemic action, it must be given by injection, by inhalation or by other adjunct modes. Over long periods no abnormal effects have been observed in animals except some slight normocytic anemia, and as much as 5 grams daily for many days has been employed in human cases without harmful effects. In earlier preparations, which probably contained a histaminelike substance, nausea, headache, malaise, rashes, joint-pains, flushing, vomiting and fever were observed. In about 10 per cent of the cases to date, however, there have been observed severe, neurotoxic reactions on the eighth nerve after the administration of from 3 to 4 grams daily; they are characterized by vertigo, tinnitus, disturbance of equilibrium and diminished auditory acuity. On cessation of therapy, partial recovery of nerve function is the rule, but this is slow, and vestibular damage seems

to be permanent. Minor toxic effects include skin rashes, mild malaise, muscular pains and drug fever.

The drug is active against a great number of gram-negative and gram-positive organisms. The most important pathogens included in these are:

GRAM-NEGATIVE

Escherichia coli
Pasteurella tularensis
Hemophilus influenzae
Pseudomonas aeruginosa
Bacillus proteus (*Proteus vulgaris*)
Salmonella typhosa
Brucella abortus

Against organisms of the latter group, it is generally less active than penicillin, but may be effective for strains that are resistant to penicillin. When administered intramuscularly, a satisfactory level in the blood of from 5 to 7 micrograms per cubic centimeter can be maintained, and it is distributed to most body fluids except those in the spinal column. Excretion is chiefly by the urine, where 50 to 80 per cent appears in 24 hours.

Streptomycin has been found very useful in a number of ways, although it has been quite disappointing in others. It is indicated in: all cases of tularemia, in which it is up to the present the most effective agent known; in infections of the urinary tract that are due to susceptible organisms; in conditions caused by the influenza organism, including meningitis, pneumonia and endocarditis; and in wound infections, bacteremias and dysenteries that are caused by susceptible organisms. Theoretically, it should be of value in treating undulant fever and typhoid fever, but failure in such cases has been the rule. In tuberculosis, it has cured most of the cases in animals, but seems of service in human beings only in certain forms of the disease, such as meningitis and peritoneal or enteric tuberculosis.

In the pulmonary form, improvement results in about 50 per cent of the cases. The drug is not incompatible with penicillin or sulfonamides and often proves useful as an adjunct treatment.

The dosage is governed by the suscepti-

GRAM-POSITIVE

Streptococcus hemolyticus
Str. viridans
Staphylococcus aureus
Staph. albus
Diplococcus pneumoniae
Bacillus anthracis
Corynebacterium diphtheriae
Mycobacterium tuberculosis

bility of the causative agent and severity of the infection. It is primarily important to give sufficient amounts to kill the organisms quickly, because acquired resistance is common and inadequate dosage can rapidly develop such a condition. The amount should be from 1 to 4 grams daily, given in divided doses every six hours. Treatment should be continued for from 48 to 72 hours after the temperature returns to normal and signs of the infection have disappeared. In tuberculous conditions, 1 to 2 grams are injected daily for a total of 120 days as an adjunct to other forms of therapy, and this may be accompanied in meningitis by intrathecal administration of 0.05 gram every other day. For intramuscular injection the powder is dissolved in sterile, pyrogen-free water or isotonic solution of sodium chloride to give a concentration of 0.1-0.2 micrograms per cubic centimeter, but for subcutaneous injection, more dilute solutions are recommended. For intravenous drip, the usual rate is 25 drops per minute of a solution of 1 to 2 grams in a liter; for intrathecal administration, it is customary to give from 10 to 20 milligrams per cubic centimeter in isotonic solution of sodium chloride. In topical applications,

solutions containing 25 to 50 milligrams per cubic centimeter may be employed.

Streptomycin Sulfate N.N.R. is packaged in vials containing activity equivalent to 1 gram of the base.

Streptomycin Hydrochloride N.N.R. is packaged in vials containing activity equivalent to 1 gram and 2 grams of the base.

Streptomycin Calcium Chloride Complex N.N.R. appears in the form of vials containing 1.3 grams, equivalent to 1 gram of the base, and in larger vials containing the equivalent of 5 grams of the base.

Dihydrostreptomycin is produced by hydrogenation of streptomycin wherein the aldehyde group is reduced to a primary alcohol. Its properties are very similar to those of the parent compound, but it has less neurotoxicity, thus permitting continuous and adequate therapy with less danger of damage to the eighth cranial nerve. It is furnished as the base or as the hydrochloride.

Neomycin⁴ was isolated from a soil organism related to *Streptomyces fradiae* and was reported by Waksman and Lechevalier in March 1949. It can be prepared under stationary or submerged conditions of culture and seems to be thermostable. It is soluble in water but not in organic solvents, is a basic compound and is most active at an alkaline pH. Up to the present writing, it has not been obtained in the crystalline form, so that little is known of its structure.

The bacterial spectrum of neomycin is similar to, but quite distinct from, that of streptomycin. The chief differences lie in the action on various strains of *Mycobacterium* and on *Escherichia coli*. Experiments to date have shown little evidence of serious toxicity to humans and of acquired resistance by organisms. The discoverers believe that it may be of considerable aid in the treatment of human tuberculosis.

TYROTHRIN

Tyrothricin N.N.R. was first separated by Dubos and his colleagues from the prod-

ucts of growth of *Bacillus brevis*, a gram-positive, aerobic, spore-forming organism isolated from soil in 1939. It was first called gramicidin, but was later found to be a mixture of two compounds that could be separated by a combination of acetone and ether. The mixture has since been called tyrothricin and the components gramicidin, which is the more active, and tyrocidine. The mixture is obtained from the culture by extracting with alcohol and precipitating with salt solution. Both of the substances are polypeptide in nature and insoluble in water but soluble in alcohol or in dilute acids. It is marketed in 10 cc. vials containing a 2 per cent solution in 92 per cent alcohol; in 1 cc. ampules containing 25 mg. in propylene glycol (75 per cent) and dilute alcohol, each of which is accompanied by a vial containing 49 cc. of sterile water and phenylmercuric borate (1:50,000); and in 10 cc. and 20 cc. ampules containing 25 mg. per cc.

Tyrothricin is effective against certain species of staphylococci, streptococci and pneumococci.⁵ Its action, at least in part, is an inhibition of enzymatic action and lysis of the bacteria. Gramicidin is powerful enough to inhibit the growth of certain streptococci in a concentration of 1:1,000,000, and a single dose of 2 micrograms intraperitoneally will protect a mouse against 1,000 times a fatal dose of pneumococci or staphylococci.

The poisonous character of the drug precludes its employment except locally. By mouth it is harmless but ineffective because of poor absorption. After injection it is destructive to the red corpuscles of the blood and leads to widespread degenerative changes in the viscera and to anemia. The lethal dose of gramicidin intravenously in mice is about 2.5 milligrams per kilogram, and daily amounts of 2 milligrams per kilogram killed dogs in from 2 to 8 days.

Tyrothricin is applied topically in any location that has no direct connection with the blood stream. It is said to be of value in treating superficial indolent ulcers when

the invading organism is gram-positive, in mastoiditis, in empyema and in infected wounds. Its field of usefulness is quite limited because it can exert no effect unless direct contact is made, and this is difficult in deeply seated infections. Saliva, urine and serum offer some inhibiting action, as do also gram-negative organisms. In cavities with no direct contact with the blood, it may be employed if caution is exercised, but proper surgical treatment must not be ignored. The use in paranasal sinuses or other infected cavities close to the subarachnoid space following surgery should be avoided because of the danger of chemical meningitis that is reported to occur under such conditions. It is applied locally to give about 500 micrograms for each cubic centimeter, but higher concentrations, which are more irritating, have been used.

Gramicidin, the chief component of tyrothricin, recently has been made available. It has the advantage over the parent mixture of being more stable and more potent. It is marketed in the form of a nasal decongestant (Graminasin) with desoxyephedrine hydrochloride, as troches (Gramozets) containing 0.25 milligram with ethyl aminobenzoate and as an ointment (Gramoderm) in a penetrating base containing 0.25 milligram of gramicidin per gram.

BACITRACIN

Bacitracin⁶ was first isolated from the products of growth of *Bacillus subtilis* (Tracy I) by Johnson, Anker and Meleney in 1945. It is produced in shallow layers in a medium containing tryptone, beef infusion, protein hydrolysate and especially digest of the soy bean; the maximum titer is obtained after 3 to 5 days of incubation. Using a synthetic medium of l-glutamic acid, however, the process gives products that are easier to concentrate and purify. The resulting aqueous infusion is decanted and extracted with normal butyl alcohol and concentrated to a gray powder by distillation under reduced pressure. The

average yield has been about 2 units per cubic centimeter, where a unit is defined as "the amount which, when diluted 1 in 1024 under particular assay conditions, . . . completely inhibits a stock strain (Chavin) of group A *Streptococcus hemolyticus*." Besides this serial dilution method of assay, a plate method has been devised, using a strain of *Corynebacterium* as the test organism.

The gray product is soluble in various alcohols and in water, but is insoluble in many of the organic solvents. It can be precipitated from concentrated aqueous solutions as the salicylate. In the dry state it is fairly stable, as it is also in concentrated solutions kept at from 0 to 5° C. for periods up to one year; at room temperature, the activity is rapidly dissipated. It can be precipitated from aqueous solution by various acids and by salts of heavy metals, but the activity is usually lost in the process. When it is dissolved in water, the active principle is diffusible through various membranes, and chemical reactions indicate that the molecular weight is low.

Absorption of bacitracin is obtained only after parenteral administration, and excretion seems to be only by the kidneys. After oral ingestion, none is detectable in the urine and very little in the feces, indicating that it is not absorbed and is largely destroyed in the gastro-intestinal tract. After subcutaneous injection, the level in the blood remains at an adequate level for about five hours, and appreciable amounts are present for as long as eight hours. The fall of activity after intramuscular or intravenous injection is more rapid, but with larger doses there is a significant amount after as long as seven hours. Whatever is excreted is found in the urine, but the amount varies widely, from 7 to 98 per cent of the dose given. It does not penetrate into the erythrocytes, and but little can be found in the spinal fluid. Its action does not seem to be inhibited by plasma, blood, pus, debris or micro-organisms.

Toxicity studies in animals show that bacitracin is comparatively safe. Oral doses as high as 3.75 grams per kilogram in mice and rats fail to bring about death, and the only untoward symptom with such a large amount is apathy. After subcutaneous injection, the lethal dose is about 0.5 to 1.5 grams per kilogram, after intraperitoneal administration, about 0.2 to 0.7 gram. The effects of large parenteral doses are hyperirritability and clonic convulsions, followed by severe depression, and autopsies reveal extensive renal necrosis in the tubules. In the experiments that have been made up to the present, it is indicated that much of the toxicity may be due to impurities, especially a histaminelike compound.

The bacterial spectrum is quite similar to that of penicillin, but there are important differences between strains. Both are chiefly active against gram-positive organisms and also gonococci and meningococci. Of the staphylococci and streptococci that have been found resistant to both penicillin and streptomycin, many succumb readily to bacitracin. In one series of infections in human beings, 30 of the isolated organisms were found more susceptible to bacitracin, only 6 to penicillin.

Therapeutically, bacitracin seems indicated as useful for many infections that resist the action of other agents. Up to the present, it has been employed chiefly by local application to boils, carbuncles, abscesses of all kinds, ulcers, sties, impetigo, conjunctivitis and osteomyelitis. The injection against systemic infections would seem a logical sequence since toxicity of the drug is low and adequate levels in the blood can be maintained with smaller doses and less frequent administration than for penicillin.

AEROSPORIN

Aerosporin⁷ (Polymixin, Bacisporin) was discovered in 1947 almost simultaneously by three separate laboratories. The group at the Wellcome Research Laboratories in

England made the most extensive investigations of the compound and gave it the name aerosporin. It is produced by the aerobic, spore-bearing *Bacillus aerosporus* (*B. polymixa*), which is grown on a half-strength broth that contains sucrose or glucose and a trace of manganese. The product is adsorbed on activated charcoal, removed by elution with diluted acetone containing sulfuric acid and purified by conversion to the helianthate and finally to the hydrochloride. The latter has been used in the freeze-dried form in most of the experiments to date and is considered fairly pure, but it still contains a substance that gives antidiuresis and one that damages the renal tubules. The latter can be removed by further purification, and the former causes little action in human beings. The purified hydrochloride is amorphous, deliquescent and soluble in water, and it is defined as containing 10,000 units per microgram. Aerosporin is a polypeptide that gives leucine, threonine and other amino acids on hydrolysis.

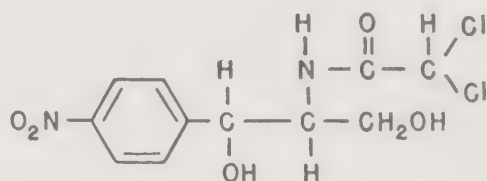
The compound is not absorbed from the gastro-intestinal tract, but the activity is transferred to the blood after parenteral administration. In the normal animal it does not enter the bile, cerebrospinal fluid or urine in a biologically active form. After a single intrathecal dose in the rabbit, it can be found in the blood for at least 24 hours. When administered by the subcutaneous or intravenous route, it disappears quickly from the blood, and the injection must be repeated at intervals of from 3 to 4 hours in order to maintain therapeutic amounts. The average intravenous lethal dose of 6.14 micrograms per kilogram in mice corresponds to levels in the blood of from 30 to 40 micrograms per cubic centimeter, which indicates that it is about 15 to 30 times as toxic as streptomycin. However, the amount of aerosporin that is necessary in the blood (0.2-0.4 micrograms per cc.) for activity is so much less that the margin of safety is apparently equal to that of streptomycin.

It is active against certain gram-negative organisms that are also susceptible to streptomycin. In experiments comparing in vivo results with those of streptomycin, penicillin and sulfadiazine, aerosporin was found superior against *Salmonella typhosa*, *S. typhimurium*, *Escherichia coli*, *Hemophilus pertussis* and *H. bronchisepticus*, about equal against *H. influenza*, and inferior against *Pseudomonas aeruginosa*. In the few clinical reports that have appeared up to the present, it would appear that aerosporin may be of greatest value in treating the early stages of whooping cough, in typhoid fever and in bacteremias due to susceptible organisms.

CHLOROMYCETIN

Chloromycetin (Chloramphenicol) was first reported by Ehrlich and his co-workers in 1947. It was isolated from the filtrate of submerged, aerated cultures of a particular strain of *Actinomyces* (*Streptomyces venezuelae*) derived from a Venezuelan soil. The product was separated by chromatography and crystallized in colorless needles or plates; it is only slightly soluble in water, but is very soluble in the lower alcohols, in acetone and in propylene glycol. It is quite stable under a variety of conditions, including a pH of from 2 to 9, and can be sterilized readily. Although the yield from cultures is very small, its activity is exhibited in a proportionately minute quantity. A successful method of synthesis was announced in March 1949 by Rebstock and her colleagues, and it has also been stated that the method lends itself to large-scale production. The structure of *d*-threo-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol is unusual for a naturally occurring organic compound because it contains an aromatic nitro radical and also is a derivative of dichloroacetic acid. The intermediate compounds in the final steps of the synthesis have been obtained in several ways, chiefly from nitroethanol and benzaldehyde

or from formaldehyde and acylaminohydroxypropionophenone. The natural product, duplicated by the final resolved product of synthesis, has the structure:



The pharmacologic, physical and chemical properties of chloromycetin seem to be satisfactory for therapeutic use. It is well absorbed by any route of administration in mice and dogs, including the oral one. The toxicity is about the same as that of streptomycin; the intravenous minimum lethal dose (50 per cent) is about 3 grams per mouse. Only small amounts are excreted in the urine after a single dose, indicating that it is used up within the body or excreted elsewhere.

Chloromycetin⁸ is active against a great variety of organisms, especially rickettsiae. Both gram-positive and gram-negative types are affected unselectively, so that a careful study of its bacterial spectrum may reveal a much wider range than is already indicated. Besides some yeasts and filamentous fungi, viruses and rickettsiae, the list already includes *M. tuberculosis* var. hominis, *Escherichia coli*, *Klebsiella pneumoniae*, *Brucella abortus*, *Salmonella typhosa*, *S. typhimurium*, *Salmonella schottmuelleri*, *Proteus* species, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Shigella dysenteriae*.

Clinical reports are very limited up to date, but a few of the possibilities are indicated. It would seem effective in Q-fever, Rocky Mountain spotted fever, scrub typhus, typhoid fever and murine typhus. Judged by preliminary studies, it may prove useful in whooping cough, undulant fever, gas gangrene and many other diseases that are resistant to penicillin and streptomycin. The dose given initially is

50 to 60 milligrams per kilogram, and subsequently 0.2 to 0.3 gram is given every 2 to 4 hours until the abatement of the disease.

AUREOMYCIN

Aureomycin⁹ was first isolated from the products of growth of *Streptomyces aureofaciens* by Duggar and reported in November 1948. It is a yellow, crystalline compound that is amphoteric and forms salts, with acids or bases, that are soluble in water, although those formed with bases are too unstable to use. At pH 8.5 with a buffer of carbonate, the sodium salt loses 12 per cent of its activity in 30 minutes and 40 per cent in two hours. The powdered drug seems to be fairly stable, and strong solutions in dextrose or saline are permanent enough to use in therapy.

The physiologic effects of administering the drug in therapeutic doses are comparatively small. In dogs no significant action has been observed on any vital functions, and the usual actions of epinephrine, acetylcholine and histamine are not influenced. Acute toxicity by oral administration in mice and rats is only obtained after 1.5-3.0 grams per kilogram. The minimum lethal dose (50 per cent) in mice and rats is about 118-134 milligrams per kilogram, and larger animals will tolerate 50 milligrams per kilogram with no symptoms except occasional vomiting. When injected subcutaneously, intramuscularly, intraperitoneally or intracutaneously, it is irritating regardless of the pH; 0.5 to 1.0 per cent solutions in the eye are also mildly irritating. After oral administration, as much as 13 per cent can be recovered from the urine during the first 55 hours. With 0.5 to 0.75 gram given daily to human beings, the maximum concentration in the urine was 256 micrograms per cubic centimeter, and the excretion continued for three or four days after the administration was stopped.

Bacteriologically and in tests on animals,

aureomycin is found to be most effective against gram-positive organisms, just as is penicillin. However, it is also active against several organisms that are resistant to penicillin or streptomycin or that are dependent on the latter, and it apparently is effective against several rickettsiae and viruses, especially those that cause disease in animals. The latter diseases include erysipelas of swine, cholera of fowl, human cholera and typhoid of fowl. In pneumonia type I, *Streptococcus hemolyticus* beta infections and general bacteremias, the drug did not seem to be quite as effective as penicillin.

Aureomycin has been studied clinically in a number of bacterial, rickettsial and viral diseases. The coccal infections responded quite well to oral administration, but in gonorrhea it seemed much inferior to penicillin. Treatment of a malignant type of brucellosis in Mexico by aureomycin was more effective than any other method, in spite of the fact that streptomycin was able to inhibit the causative agent to a greater degree in vitro. It was also the only drug that appeared adequate in 200 cases of ocular infections by both gram-positive and gram-negative organisms. The most striking results, however, have been obtained in rickettsial and viral diseases, even when the drug was not effective against the causative agent in vitro. The diseases include Rocky Mountain spotted fever, typhus, scrub typhus, Q-fever, lymphogranuloma venereum, granuloma inguinale, virus pneumonia, rickettsial pox and psittacosis (parrot fever). It also has been successful in scarlet fever, whooping cough and tularemia. Indeed, one physician has claimed that it has the widest therapeutic range of any antibiotic.

The dosage employed is at present in the experimental stage. In brucellosis, a total of 0.1 gram was given in four parts the first day, 0.6 gram the second, 1.6 gram the third and 2.0 grams the fourth, and the program was continued for ten days. In

ocular infections, it was applied in 0.5 per cent solution as the borate.

Toxic reactions have been mild and occasional, but the experience has been rather limited, and judgment of dangers must be reserved temporarily. The main effects that have been noted are nausea and vomiting, diarrhea and loss of appetite. Occasionally, mild drowsiness has been reported and one or two cases of drug rash have been noted. In no instance were any of these severe enough to warrant stopping administration.

OTHER COMPOUNDS

Because of the limitations of space, it would be impossible to give here the details of all antibiotics that have been described. Mention is made frequently in the literature that a given culture of some organism shows antagonism to certain other organisms, many of which are pathogens. It is probable that at least some of these will be submitted to further study and may be proven useful in medicine. Besides the ones that already have been described here, nearly 100 have at least received a name; in some cases the structure has been determined, and several have been synthesized. Most of them have received scant attention because they are unpromising in some respect, but many of them are still being studied. In 1948, more than a dozen new products were added to the list, and a continuing and possibly increasing activity toward finding new antibiotics can be expected.

The following list gives a brief description of many that have been named. Included are some from higher plants, because they have been called antibiotics, although they are not comprised in the definition that was given at the beginning of this chapter; there might have been included such substances as juglone (1856) and chlorophyll, which have been called antibiotics. The list is given in chronological order for the sake of historical interest. The structure has been determined for those compounds marked with an asterisk.

- 1889 Pyocyanase—*Pseudomonas aeruginosa* by Bouchard; a mixture containing weakly active acids.
- 1896 *Mycophenolic Acid—*Penicillium brevi-compactum* by Gosio (Revista d'Igiene 7:825); $C_{17}H_{20}O_6$.
- 1911 *Chlororaphine—*Bacillus chlororaphis* by Laseur (Dissertation, Nancy); $C_{26}H_{20}N_6O_2$.
- 1912 *Kojic Acid—*Aspergillus oryzae* by Saito (Ch. Abs. 7:2191); $C_7H_6O_4$.
- 1912 *Penicillic Acid—*Penicillium puberulum* by Alsberg and Black (Bull. Plant Ind. 270:7-48); $C_8H_{10}O_4$.
- 1922 Lysozyme—animal tissues by Fleming (Proc. Roy. Soc. 93B:306); an enzyme.
- 1924 Actinomycetin—*Actinomyces* sp. by Gratia and Dath (Compt. rend. 91:1442); a polypeptide.
- 1924 *Pyocyanine — *Pseudomonas aeruginosa* by Wrede and Strack (Ztschr. f. Physiol. Chem. 140:1-15); $C_{26}H_{24}N_4O_2$.
- 1927 Violacein — *Chromobacterium violaceum* by Riley and Pyne (Biochem. J. 21:1059); $C_{42}H_{28}N_6O_7$.
- 1929 *Penicillin—*Penicillium notatum* by Fleming (Brit. J. Exper. Path. 10:226); $C_{16}H_{18}N_2O_4$.
- 1930 Lactenin—milk by Jones and Simms (J. Exper. Med. 51:327); stable protein.
- 1931 *Citrinin—*Penicillium citrinin* by Hetherington and Raistrick (Trans. Roy. Soc. 220B:269); $C_{12}H_{14}O_5$.
- 1932 { *Puberulic Acid—*Penicillium aurantiovirens* by Birkinshaw and Raistrick (Biochem. J. 26:441); $C_8H_6O_6$ and $C_8H_4O_6$.
- 1933 Diplococcin—*Streptococcus* sp. by Whitehead (Biochem. J. 27:1793).
- 1936 *Erdin—*Aspergillus terreus* by Raistrick and Smith (Biochem. J. 30:1315); $C_{16}H_{10}Cl_2O_7$.
- 1936 *Geodin—*Aspergillus terreus* by Raistrick and Smith (Biochem. J. 30:1315); $C_{17}H_{12}Cl_2O_7$.
- 1936 *Gliotoxin—*Gliocladium fimbriatum* by Weindling and Emerson (Phytopathology 26:1068); $C_{13}H_{14}N_2O_4S_2$.
- 1939 *Fumigatin—*Aspergillus fumigatus* by Anslow and Raistrick (Biochem. J. 32:687); $C_8H_8O_4$.
- 1939 { Tyrothricin—*Bacillus brevis* by Hotchkiss and Gramicidin Dubos (J. Biol. Chem. 132:791); Tyrocidine $C_{44}H_{63}N_9O_{11}$ and $C_{74}H_{106}N_{14}O_4$.
- 1939 Griseofulvin—*Penicillium griseo-fulvum* by Oxford *et al.* (Biochem. J. 33:240); $C_{17}H_{17}ClO_6$.
- 1939 Iodin—*Chromobacterium iodinum* by Davis (Zentr. Bact. Parasitenk. II Abt. 100:273); $C_{12}H_8N_2O_4$.
- 1939 Simplexin—*Bacillus simplex* by Cordon and Haensler (Soil Science 47:207).
- 1940 Actinomycin A and B—*Actinomyces antibioticus* by Waksman and Woodruff (Proc. Soc. Exper. Biol. & Med. 45:609); $C_{41}H_{56}N_8O_{11}$.
- 1942 Fumigacin (Helvolic Acid)—*Aspergillus fumigatus* by Waksman *et al.* (Science 96:202); $C_{29}H_{40}O_7$.

- 1942 Gigantic Acid (Flavicin)—*Aspergillus giganteus* by Wilkins and Harris (Brit. J. Exper. Path. 23:166; see also Bush and Goth: J. Pharmacol. 78:164).
- 1942 Notatin (Penicillin B, Penatin)—*Penicillium notatum* by Raistrick *et al.* (Nature 150:634; see also Doisy *et al.*: J. Biol. Chem. 148: 1365 and Kocholaty: Science 97:186).
- 1942 *Clavacin (Claviformin, Patulin, Expansin)—*Aspergillus clavatus* by Waksman *et al.* (Science 96:202; see also Chain *et al.*: Brit. J. Exper. Path. 23:202; Raistrick *et al.*: Lancet 2:625; Nauta *et al.*: Rec. trav. chim. 64:254); $C_7H_6O_4$.
- 1942 Penicidin—*Penicillium* sp. by Atkinson (Austrian J. Exper. Biol. & M. S. 20: pt. 4, 287).
- 1942 Protoactinomycin—*Protoactinomyces* sp. by Gardner and Chain (Brit. J. Exper. Path. 23:123).
- 1942 *Spinulosin—*Penicillium spinulosum* by Raistrick and Anslow (Biochem. J. 32:803); $C_8H_8O_5$.
- 1942 Streptothricin—*Actinomyces lavendulea* by Waksman and Woodruff (Proc. Soc. Exper. Biol. & Med. 49:207); protein.
- 1943 Aspergillilic Acid—*Aspergillus flavus* by White and Hill (J. Bact. 45:433); $C_{12}H_{20}N_2O_2$.
- 1943 Chlorellin—*Chlorella vulgaris* by Pratt (Am. J. Bot. 30:32).
- 1943 Corylophilin—*Penicillium corylophilum* by Penau *et al.* (Bull. Soc. Chim. Biol. 25:406).
- 1943 Flavacidin—*Aspergillus flavus* by McKee and MacPhillamy (Proc. Soc. Exper. Biol. & Med. 53:247).
- 1943 Gladiolic Acid—*Penicillium gladioli* by Brian *et al.* (Nature 157:697).
- 1944 *Streptomycin—*Streptomyces griseus* by Schatz *et al.* (Proc. Soc. Exper. Biol. & Med. 55: 66); $C_{21}H_{39}N_7O_{12}$.
- 1944 Actidione—*Streptomyces griseus* by Schatz and Waksman (Proc. Soc. Exper. Biol. & Med. 57:244; see also Whiffen: J. Bact. 54:41); $C_{27}H_{42}N_2O_7$.
- 1944 *Allicin—*Alium sativum* (garlic) by Cavallito and Bailey (J. Am. Chem. Soc. 66:1950); $C_6H_{10}OS_2$.
- 1944 Aspergillin—*Aspergillus* sp. by Stanley (Austrian J. Sci. 6:151).
- 1944 Canavalin—*Canavalia ensiformis* by Farley (Surg., Gynec. & Obst. 79:83); an enzyme.
- 1944 Chetomin—*Chaetomium cochliodes* by Waksman and Bugie (J. Bact. 48:527).
- 1944 Crepin—*Crepis taraxicifolia* (Thuill.) by Hartley (Brit. J. Exper. Path. 25:208); $C_{14}H_{16}O_4$.
- 1944 *Gentisyl Alcohol—*Penicillium patulum* by Birkinshaw *et al.* (Biochem. J. 37:726); $C_7H_8O_3$.
- 1944 { Gramicidin C—*Bacillus brevis* by Gause *et al.*
Gramacidin S—(Compt. rend. U.S.S.R. 53: 217; Am. Rev. Soviet Med. 2:134).
- 1944 Mycetin—*Actinomyces violaceus* by Fain- schmidt and Korenyako (Biokhimiya 9:147).
- 1944 Subtilin—*Bacillus subtilis* by Jansen and Hirschmann (Arch. Biochem. 4:297).
- 1945 Bacitracin—*Bacillus subtilis* by Johnson *et al.* (Science 102:376).
- 1945 Clitocybine—*Clitocybe* sp. by Hollande (Compt. rend. 221:361).
- 1945 Glutinosin—*Metarrhizium glutinosum* by Brian and McGowan (Nature 157:334).
- 1945 Lateritin—*Fusarium lateritium* by Cook *et al.* (Brit. J. Exper. Path. 26:404); $C_{24}H_{42}N_2O_6$.
- 1945 Mycocidin—an *Aspergillaceae* by Gerber and Gross (Science 101:116).
- 1945 Prodigiosin—*Chromobacterium prodigiosum* by Wrede and Rothaas (Ztschr. f. Physiol. Chem. 226:95).
- 1945 Tomatin—*Lycopersicon esculentum* by Irving *et al.* (Science 102:9).
- 1945 Viridin—*Trichoderma viride* by Brian and McGowan (Nature 156:144).
- 1946 Bacillin—*Bacillus subtilis* by Foster and Woodruff (J. Bact. 51:363).
- 1946 Colistatin—*Bacillus* sp. by Gause (Science 104: 289).
- 1946 Erythrin—blood by Zil'ber and Yakobson (Zur. mikrobiol. epidemiol. immunobiol. No. 12:3).
- 1946 Eumycin—*Bacillus subtilis* by Johnson and Burdon (J. Bact. 51:591).
- 1946 Grisein—*Streptomyces griseus* by Waksman *et al.* (J. Bact. 51:753).
- 1946 *Javanicin—*Fusarium javanicum* by Arnstein *et al.* (Nature 157:333); $C_{15}H_{14}O_6$.
- 1946 Lactaroviolin—*Lactarius deliciosus* by Willstaedt and Zetterberg (Svensk. Kem. Tidj. 58:306); $C_{15}H_{14}O$.
- 1946 Licheniformin—*Bacillus licheniformis* by Cal- low and Hart (Nature 157:334).
- 1946 Litmocidin—*Proactinomyces cyaneus antibiot- icus* by Gause (J. Bact. 51:649); an antho- cyanidin.
- 1946 Phthiacol—*Mycobacterium tuberculosis* by Lichstein and Van de Sand (J. Bact. 52:145).
- 1946 Polyporin—*Polystictus sanguineus* by Rose (Nature 158:292).
- 1946 Protoanemonin—*Anemone pulsatilla* by Baer *et al.* (J. Biol. Chem. 162:65).
- 1946 { Subtilysin—*Bacillus subtilis* by Valee
Endosubtilysin (Rec. med. vet., see Chem. Abs. 40:4104).
- 1946 Ustin—*Aspergillus ustis* by Doering *et al.* (J. Am. Chem. Soc. 68:725); $C_{19}H_{15}Cl_3O_5$.
- 1947 Actinorubin—*Actinomyces* sp. by Kocholaty (J. Biol. Chem. 168:754).
- 1947 { Bioformin—*Polyporus biformis* by Rob-
Bioforminic Acid bins *et al.* (Proc. Nat. Acad. Sci. 33:176).
- 1947 Aerosporin (Polymixin)—*Bacillus aerosporus* (*B. polymixa*) by Brownlee and Bushby (Lancet 254:127; see also Stanley and Schlosser: J. Bact. 54:549).
- 1947 Chloromycetin—*Streptomyces venezuelae* by Ehrlich *et al.* (Science 106:417); $C_{11}H_{12}Cl_2N_2O_5$.

- 1947 Enniatin A—(see Lateritin).
- 1947 Enniatin B—*Fusarium orthoceras* var. Enniatinum by Gäumann *et al.* (*Experientia* 3:202).
- 1947 Lavendulin—*Streptomyces lavendulae* by Kocholaty (*J. Biol. Chem.* 168:754).
- 1947 Nocardine—*Nocardia colliaca* by Emmart (*Rep. Antibiotic Study Sec.*).
- 1947 Pleurotin—*Pleurotus griseus* by Robbins *et al.* (*Proc. Nat. Acad. Sci.* 33:171).
- 1947 Raphanin—Radish seeds by Ivanovics and Horvath (*Nature* 160:297).
- 1947 Streptolin—*Streptomyces* sp. by Rivett and Peterson (*J. Am. Chem. Soc.* 69:3006).
- 1947 Sulfactin—*Actinomyces* sp. by Kocholaty *et al.* (*J. Biol. Chem.* 168:765).
- 1947 Tardin—*Penicillium tardum* by Borodin *et al.* (*Brit. J. Exper. Path.* 28:31).
- 1948 Aureomycin—*Streptomyces auriofaciens* by Duggar (*Science News Letter* 54, 69, July 31).
- 1948 Musarin—*Actinomyces* sp. by Arnstein *et al.* (*J. Gen. Microbiology* 2:111); $C_{35}H_{60}N_2O_{14}$.
- 1948 Mycelianamide—*Penicillium griseo-fulvum* by Oxford and Raistrick (*Biochem. J.* 42:323); $C_{22}H_{28}N_2O_5$.
- 1948 Subtenolin—*Bacillus subtilis* strain by Hirshhorn *et al.* (*Proc. Soc. Exper. Biol. & Med.* 67:429).
- 1948 Subtilin C—*Bacillus subtilis* strain ATCC by Hassall (*Nature* 161:317).
- 1948 Trichothecin—*Trichothecium roseum* by Freeman and Morrison (*Nature* 162:30).
- 1948 Xanthomycin—*Streptomyces* sp. by Thorne and Peterson (*J. Biol. Chem.* 176:413).

- 1949 Neomycin—*Streptomyces fradiae* by Waksman and Lechevalier (*Science* 109:305).

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28

Vitamins

VITAMIN A

THE VITAMINS D

VITAMIN C

THIAMINE HYDROCHLORIDE

RIBOFLAVIN

INOSITOL

BIOTIN

ANTIHEMORRHAGIC VITAMINS

THE VITAMINS E

PANTOTHENIC ACID

PYRIDOXINE

NICOTINIC ACID

FOLIC ACID

VITAMIN B₁₂

p-AMINOBENZOIC ACID

In 1905 Pekelharing and in 1906 Hopkins pointed out that in addition to proteins, fats, carbohydrates and minerals, a small amount of milk was necessary to maintain animal life. Hopkins concluded that milk contained "accessory food factors." The word "vitamine" was first coined by Funk in 1912 to describe the substance that was present in rice polishings (Eijkman's antiberiberi factor) and in foods that cured polyneuritis in birds and beriberi in man. Because the antiberiberi substance contained nitrogen, it was thought to be an amine. This, in addition to its being necessary for life, gave rise to the term "vitamine," in which the prefix vita means life. Later investigations revealed the presence of other "accessory food factors" or "vitamines" that did not contain nitrogen and hence Drummond's suggestion to drop the terminal "e" was accepted.

Symptoms or diseases in humans, that we

know today are due to nutritional deficiencies of vitamins, have been described or known for centuries. Some of these have been described under the names beri-beri, scurvy, rickets, pellagra and night blindness.

All known naturally occurring vitamins are synthesized by plants, with the exception of the vitamins D and vitamin A; however, precursors (provitamins) in these two cases are also synthesized by plants. In some cases some animals and birds can synthesize some of the vitamins and provitamins such as vitamin C and 7-dehydrocholesterol.

Vitamins are arbitrarily classified according to their solubility in water and fats, e.g., fat-soluble A, D, E and K and the water-soluble B₁, B₂, B₆, C, nicotinic acid, folic acid, pantothenic acid, biotin, inositol and *p*-aminobenzoic acid.

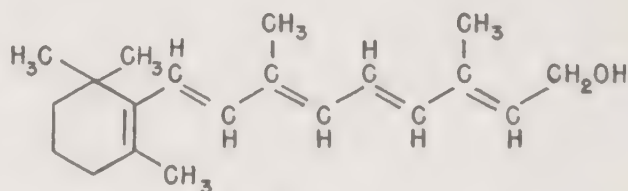
Vitamins can be administered in doses far exceeding the daily requirement with no ap-

parent untoward effects. The intake of the water-soluble vitamins in excess of that needed by the body is excreted in the urine. The amounts of vitamins found in the urine furnishes a means of measuring the vitamin reserves in the body. The fat-soluble vitamins usually are stored in the liver and thus the body is able to conserve these factors.

VITAMIN A

About 1913, McCollum and Davis,¹ and Osborne and Mendel² showed that rations of purified casein, carbohydrates, various salt mixtures, and lard induced an apparent normal growth in experimental animals for periods that varied from 70 to 120 days, after which time little or no increase in body weight could be induced. The resumption of growth occurred quite promptly upon addition to the diet of the ether extract of egg or butter. The factor responsible for this growth was called "fat-soluble A" to distinguish it from the "water-soluble B." Therefore, it was called vitamin A. Further work showed this factor to be present in cod-liver oil,³ but not in lard, olive, corn, cottonseed, linseed, soya bean or almond oils.⁴ McCollum and Davis,⁴ in 1914, showed that this factor could be concentrated in the nonsaponifiable portion of butter oil. It was shown to be absent from cereal grains, seeds, etc., whereas alfalfa and cabbage leaves were found to be excellent sources of the vitamin. Furthermore, ether extracts of spinach leaf or clover were shown to be rich in vitamin A. In about 1919, Steenbock⁵ pointed out that the vitamin A potency of certain plant sources seemed to run parallel with the amount of yellow fat-soluble pigments present in them. He prepared⁶ nonsaponifiable concentrates from carrots, alfalfa and yellow corn. He suggested that vitamin A activity might be associated with the "carotenoid pigments." Because cod-liver oil concentrates (nonsaponifiable portion) are essentially colorless but very potent in vitamin A activity, Steenbock stated that the vitamin A of animals might be a colorless

or leuco form of carotene. In 1928, von Euler⁷ noted that substances that were rich in vitamin A gave certain chemical color tests similar to those given by carotene. He demonstrated that carotene was active when fed to vitamin A deficient rats. Moore, in 1930, showed that ingested carotene is converted to vitamin A by the rat.⁸ This established the relationship to the active yellow carotenes of plants and the nearly colorless, highly active vitamin concentrates from liver oils. Karrer,⁹ who had previously determined the constitution of beta-carotene, suspected a structural relationship between certain carotenes and vitamin A. He degraded, by ozonization, an impure preparation of vitamin A obtained from halibut-liver oil and obtained geronic acid in an amount that indicated the presence of one beta-ionone ring. Two years later, the carbon skeleton of vitamin A was established by the synthesis, starting from beta-ionine, of perhydrovitamin A.¹⁰ Knowing that beta-carotene has a conjugated system of 11 double bonds and that vitamin A also contained a system of 5 conjugated double bonds and a primary alcohol group, Karrer proposed the following structural formula for vitamin A.



Vitamin A

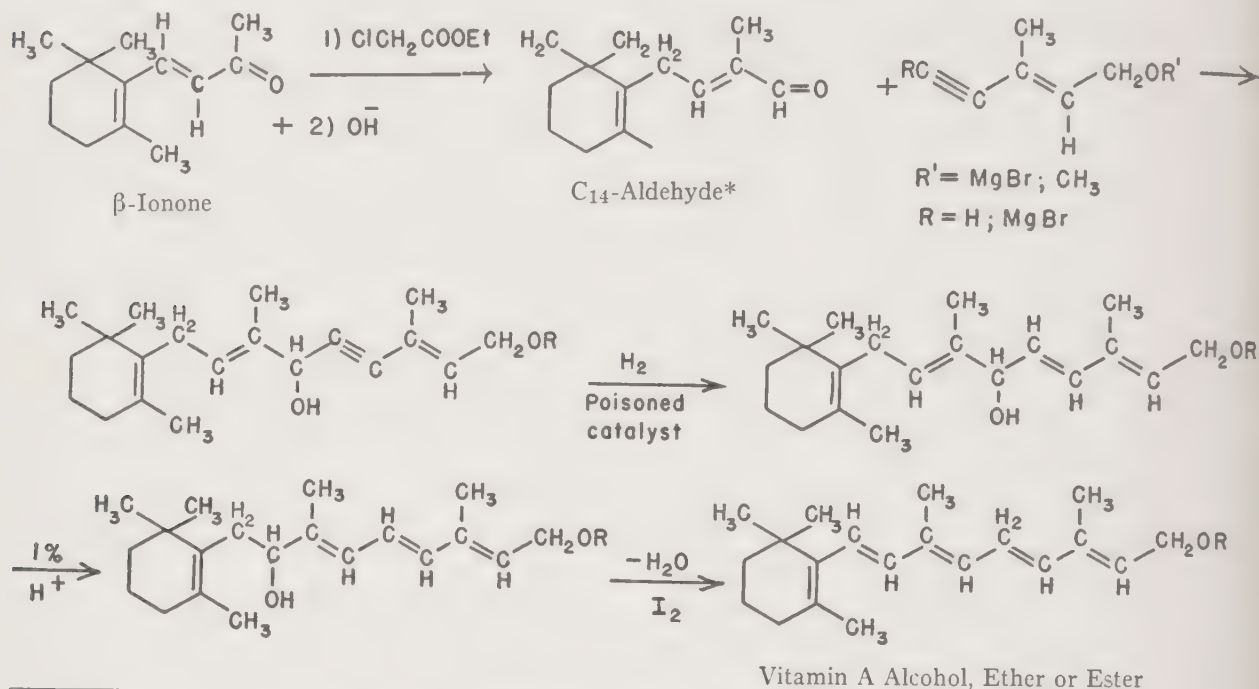
Vitamin A exists in two forms which seem to be geometric isomers, i.e., vitamin A, m. p. 63-64° C. and neovitamin A, m. p. 59-60° C. The two forms have about the same biologic activity and each can be converted into mixtures of the two by iodine catalysts on the anthraquinonecarboxylic ester. Most liver oils contain vitamin A and neovitamin A in the ratio of 2 to 1.

Disregarding stereochemical variations, a number of compounds with structures corresponding to vitamin A, its ethers and its

esters have been prepared.¹¹ These compounds, as well as a synthetic vitamin A acid, possess biologic activity. Some of these compounds have been prepared as follows.^{12,13,14}

oxidized fats and oils. It can be protected by the exclusion of air and light and by the presence of antioxidants.

Like all substances that have a polyene



* Note the shift of the double bond in the preparation of this aldehyde.

Although fish-liver oils are used as such for their vitamin A content, purified or concentrated forms of vitamin A are of great commercial significance. These are prepared in three ways: (1) saponification of the oil and concentration of the vitamin A in the nonsaponifiable matter by solvent extraction, the product is marketed as such; (2) molecular distillation of the nonsaponifiable matter, from which the sterols have previously been removed by freezing, giving a distillate of vitamin A containing 1,000,000 to 2,000,000 I. U. per gram; (3) subjecting the fish oil to direct molecular distillation to recover both the free vitamin A and vitamin A palmitate and myristate.

Pure crystalline vitamin A occurs as pale yellow plates or crystals. It melts at 63–64° C. and is insoluble in water, but soluble in alcohol, the usual organic solvents and the fixed oils. It is unstable in the presence of light and oxygen and in oxidized or readily

structure, vitamin A gives color reactions with many reagents, most of which are either strong acids or chlorides of polyvalent metals. An intense blue color (Carr-Price) is obtained with vitamin A in dry chloroform solution upon the addition of a chloroform solution of antimony trichloride. This color reaction has been studied intensively and is the basis of a colorimetric assay for vitamin A.¹⁵

The chief source of vitamin A is fish-liver oils, which vary greatly in their content of this vitamin (see Table 52). It occurs free and combined as the biologically active esters, chiefly of palmitic and some myristic and dodecanoic acids. It is also found in the livers of animals, especially those which are herbivorous. Milk and eggs are fair sources of this vitamin. The provitamins A, e.g., beta, alpha and gamma carotenes and cryptoxanthin, are found in green parts of plants,

TABLE 52. VITAMIN A CONTENT OF SOME FISH LIVER OILS

SOURCE OF OIL	ANIMAL	POTENCY (I.U./GM.)
Halibut, liver	<i>Hippoglossus hippo-</i> <i>glossus</i>	60,000
Percomorph, liver	Percomorph fishes (mixed oils)	60,000
Shark, liver	<i>Galeus zygopterus</i>	25,500
Shark, liver	<i>Hypoprion brevirostris</i> and other varieties ...	16,500
Burbot, liver	<i>Lota maculosa</i>	4,880
Cod, liver	<i>Gadus morrhua</i>	850

carrots, red palm oil, butter, apricots, peaches, yellow corn, egg yolks, etc. The provitamins aphanin and myxozanthin are found in sea algae. The carotenoid pigments are poorly utilized by humans, whereas animals differ in their ability to utilize these compounds. These carotenoid pigments are provitamins A because they are converted, in part in the liver, to the active vitamin A. This, because cleavage of the molecule at the double bond in the middle, and conversion of this terminal carbon atom to a primary alcohol group, can in the case of β -carotene give rise to two molecules of vitamin A, whereas in the other three carotenoids only one molecule of vitamin A is possible by this transformation. These carotenoids have only one ring (see formula for β -carotene) at the end of the polyene chain that is identical to that found in β -carotene and is necessary and found in vitamin A.

The conjugated double bond systems found in vitamin A and β -carotene are necessary for activity, for when these compounds are partially or completely reduced, activity is lost. The ester and methyl ethers of vitamin A have a biologic activity on a molar basis equal to vitamin A. Vitamin A acid is biologically active but is not stored in the liver. Oxidation products of β -carotene in which one β -ionone ring is still intact, together with a major portion of the polyene side chain, possess vitamin A activity. Some of these products are β -semicarotenone, β -

apo-2-carotinal (its reduction product, also β -apo-2-carotinol), and β -apo-4-carotinal. The oxidation product β -carotene-oxide is also active. Kitol, a substance obtained from the nonsaponifiable portion of whale oil after the removal of vitamin A, has no activity as such, but upon pyrolysis yields some vitamin A. Highly purified kitol analyzes for the formula $C_{40}H_{58}(OH)_2$.

Vitamin A is often called the "growth vitamin" because a deficiency of it in the diet causes a cessation of growth in young rats.* A deficiency of vitamin A is manifested chiefly by a degeneration of the mucous membranes throughout the body. This degeneration is evidenced to a greater extent in the eye than in any other part of the body and gives rise to a condition known as xerophthalmia. The eyes become hemorrhagic, incruited, infected, and this is accompanied by a dryness of the conjunctivae. It is associated with atrophy of the para-ocular glands, with metaplasia of the epithelium of the glands and conjunctivae and with loss of sensation in the conjunctiva, especially affecting the cornea. At first, the dryness may be associated with photophobia. Triangular white spots (Bitot's spots) appear in the palpebral fissure; irregular wrinkled patches of xerosis are found over the bulbar conjunctivae and later over the cornea. A characteristic light-brown pigmentation develops in the conjunctiva. The superficial layers of the cornea degenerate. In the final stage, corneal softening or keratomalacia develops, with resulting severe impairment of vision. Permanent blindness is likely to follow. In the earlier stages of vitamin A deficiency, there may develop a night blindness (nyctalopia) which can be cured by vitamin A. Night blindness can be defined as the inability to see in dim light. Vitamin A deficiency that leads to night blindness and total blindness is especially common in India, China, Yucatan, Java, Sumatra and

* This property is used as the basis for the quantitative assay of vitamin A-containing substances.

the Malay States. It has been observed in prisoners, slaves and workmen and in the people of Denmark during World War I.

"Dark adaption" or "visual threshold" is a more suitable description than "night blindness" when applied to many subclinical cases of vitamin A deficiency. The visual threshold at any moment is just that light intensity required to elicit a visual sensation. Dark adaption is the change which the visual threshold undergoes during a stay in the dark after an exposure to light. This change may be very great. After exposure of the eye to daylight, a stay of thirty minutes in the dark results in a decrease in the threshold by a factor of a million. This phenomenon is used as the basis to detect subclinical cases of vitamin A deficiencies. These tests vary in their technic, but essentially measure visual dark adaption after exposure to bright light and compare it with the normal.¹⁶

Advanced deficiency of vitamin A gives rise to a dryness and scaliness of the skin, accompanied by a tendency to infection. Characteristic lesions of the human skin due to vitamin A deficiency usually occur in sexually mature persons between the ages of sixteen and thirty and not in infants. These lesions appear first on the anterolateral surface of the thigh and on the posterolateral portion of the upper forearms and later spread to adjacent areas of the skin. The lesions consist of pigmented papules, up to 5 mm. in diameter, at the site of the hair follicles.

In the rat, marked vitamin A deficiency leads to a degeneration of the testes of the male, accompanied by sterility in three months. In the female rat, the vaginal mucous membrane becomes permanently cornified, and the ovaries also are affected.

The mode of action of vitamin A in the deficiency symptoms described above is not definitely known. However, vitamin A also plays a role in vision¹⁷ that can be explained as follows. The modern duplicity theory considers the vertebrate retina as a double

sense organ in which the rods are concerned with colorless vision at low light intensities and the cones with color vision at high light intensities. A dark-adapted, excised retina is rose-red in color and, when it is exposed to light, its color changes to chamois, to orange, to pale-yellow, and finally upon prolonged irradiation it becomes colorless. The rods contain photosensitive visual purple (rhodopsin) which, when acted upon by light of a definite wave length, is converted to visual yellow and initiates a series of chemical steps necessary to vision. Visual purple is a conjugated, carotenoid protein having a molecular weight of about 270,000 and 10 prosthetic groups per molecule. It has an absorption maximum of about 510 mμ. The prosthetic group is probably retinene (not like any known carotenoid) or some immediate precursor because light acting upon dark-adapted retinas loosens the bond between retinene and the protein. This because the orange yellow color that develops is completely soluble in petroleum ether, whereas this solvent has no effect upon the retinene in dark-adapted retinas that have not been exposed to light. Chloroform can exert the same effect as light, with the subsequent solution of the retinene in chloroform. The retinene in visual purple is converted into colorless vitamin A upon prolonged exposure to light. Petroleum ether will dissolve the vitamin A that is generated in this fashion. The above conversion of retinene to vitamin A is a reversible one, and the greatest amounts of vitamin A are converted to retinene in the dark. The function of retinene in visual purple is to provide an increased absorption coefficient in visible light and thus sensitize the protein which is denatured. This process initiates a series of physical and chemical steps necessary to vision. The protein itself differs from other proteins by having a lower energy of activation, which permits it to be denatured by a quantum of visible light. Other proteins require a quantum of ultraviolet light to be denatured. The bond between the pigment and

protein is much weaker when the protein is denatured than when it is native. The denaturation process of the protein is reversible and takes place more readily in the dark to give rise, when combined with retinene, to visual purple. The effectiveness of the spectrum in bleaching visual purple runs fairly parallel with its absorption spectrum (510 mμ) and with the sensibility distribution of the eye in the spectrum at low illuminations. It has been calculated that for man to see a just perceptible flash of light, in a dark-adapted eye, there need be transformed photochemically only one molecule of visual purple in each 5 to 14 rod cells. In vivo, visual purple is constantly re-formed as it is bleached by light, and, under continuous illumination, an equilibrium between visual purple,* visual yellow,† and visual white‡ is maintained. If an animal is placed in the dark, the regeneration of visual purple continues until a maximum concentration is obtained. Visual purple in the eyes of an intact animal may be bleached by light and regenerated in the dark an enormous number of times.

Visual purple has been found in the whole vertebrate series from *Petromyzon* to man. It is not evenly distributed over the retina. It is missing in the fovea, and in the regions outside of the fovea its concentration undoubtedly increases to a maximum in the region about 20° off center, corresponding to the high density of rods in this region. Therefore, in order to see objects best in the dark, one should not look directly at the object.

Pure vitamin A has the activity of 3,500,000 I. U. per gram. The average daily requirements for vitamin A are 3,000 I. U. for infants and 5,000 I. U. for adults; 10,000 to 20,000 I. U. per day for humans would appear to be more effective as a daily requirement. Moderate to massive doses of vitamin A have been used in pregnancy, lac-

tation, acne, abortion of colds, removal of persistent follicular hyperkeratosis of the arms, persistent and abnormal warts, corns and callouses, etc. Phosphatides or the tocopherols enhance the absorption of vitamin A.

THE VITAMINS D

The first full description of rickets was published in a treatise by Francis Glisson, in 1650, an English professor at Cambridge. This deficiency disease is most common in northern countries, especially in large cities, whereas it is fairly rare in southern countries. The idea that rickets was connected with nutrition began to develop in the last quarter of the nineteenth century. In about 1890, Palm,¹⁸ an English medical man, first pointed out that rickets is prevalent where there is little sunlight and quite rare wherever sunshine is abundant. He recommended the use of sunlight in the treatment of rickets. J. Raczyński,¹⁹ in 1913, exposed puppies to sunlight to see if he was able to increase the amount of mineral substances in their bones and, from his results, concluded that sunlight plays a principal role in the etiology of rickets. In 1919-1920, Huldschinsky²⁰ reported that ultraviolet light cured rickets in children. Hess and Unger,²¹ in 1921, confirmed this observation and demonstrated that sunshine would exert the same effect. Although cod-liver oil had long been used, and as early as 1848, recommended for adult rickets and later for rickets in children, it was not accepted by many in the fields of medicine until laboratory experiments with animals demonstrated its value in this deficiency disease.

In 1919, Mellanby²² prevented rickets in puppies by the inclusion of cod-liver oil or butterfat in the diet. McCollum *et al.*²³ (1921-1922) reported that this factor was distinct from vitamin A. It was also recognized by these and other workers²⁴ that calcium and phosphorus were also necessary in the prevention and cure of rickets. McCollum *et al.*²⁵ (1922) furnished clear evi-

* Protein combined with retinene.

† Protein denatured plus free retinene.

‡ Protein plus vitamin A.

dence of the existence of vitamin D as an entity distinct from vitamin A.

During the period from 1921 to 1924, reports from laboratories showed that irradiation of the body with light rays of short wave length in the region of 300 mμ from sunlight, mercury vapor quartz lamps or from carbon arc lamps promoted growth and improved ossification in children and experimental animals when the ratio of calcium and phosphorus in the diet was not conducive to normal development of bones.

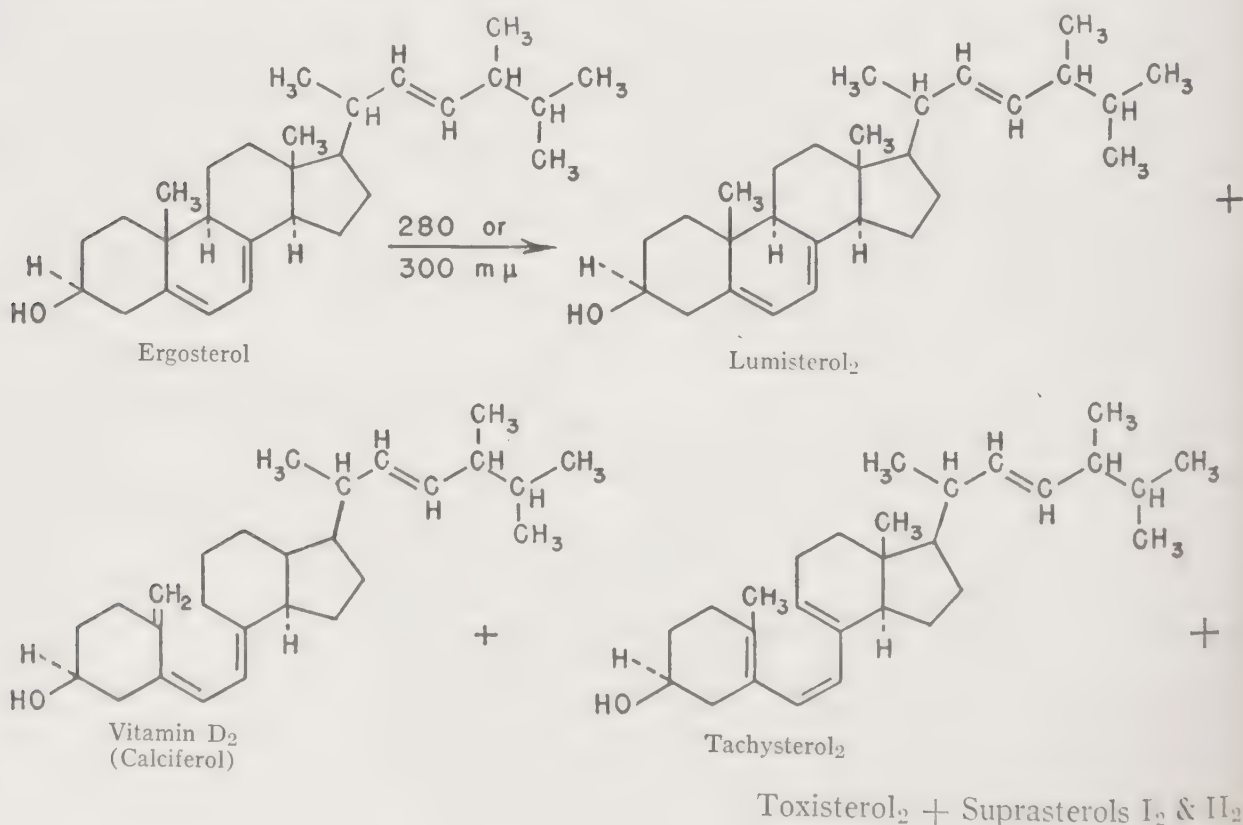
Hess²⁶ and Steenbock,²⁷ working independently, in 1924 reported that the irradiation of foods including oils confers antirachitic properties upon them. It was also shown that the irradiation of highly purified phytosterol or cholesterol gave an antirachitic product.²⁸ Phytosterol and cholesterol when purified via their dibromides²⁹ could not be activated. This indicated the presence of small quantities of activatable substances in what was previously thought to be pure cholesterol and

phytosterol. Because ergosterol* was thought to be one of the impurities that might possibly be activatable, it was irradiated, and the resultant irradiation product was shown to have exceedingly potent antirachitic properties.³⁰

The course of the irradiation of ergosterol is not a simple one. The solvent employed, the time of exposure and the wave length of light employed determine the nature and amounts of the end-products obtained. Under the best conditions, nearly 50 per cent of a vitamin D (now designated as vitamin D₂) is obtained, together with tachysterol₂ and lumisterol₂, accounting for most of the remainder. Some suprasterols I₂ and II₂ and toxisterol₂ are formed. When ultraviolet rays of about 300 mμ are employed, a predominance of lumisterol₂ and vitamin D₂ are obtained, whereas, shorter rays of about 280 mμ give rise to a predominance of tachysterol₂ and vitamin D₂.

* Detected by absorption spectrum data before and after irradiation and by its sensitivity toward oxida-

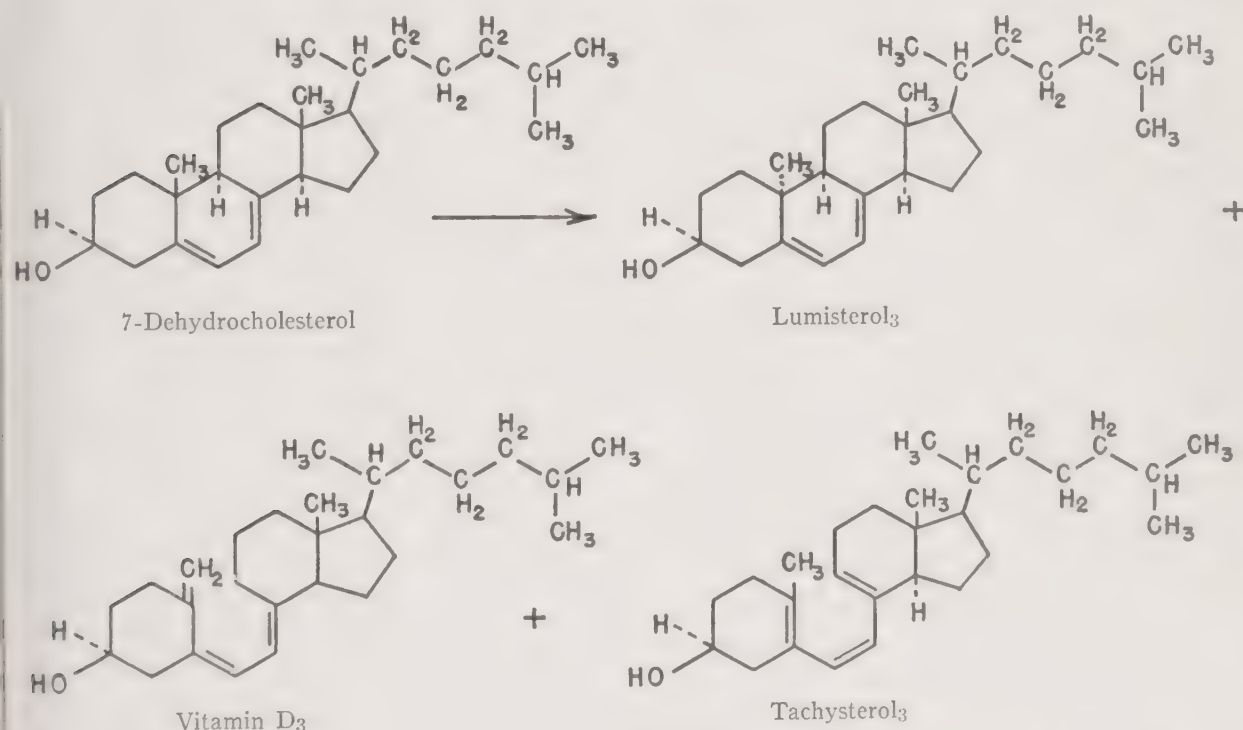
tion as compared to the purified (via dibromide) and nonpurified cholesterol and phytosterol.



Ergosterol and other 7-dehydrosterols also can be converted into vitamins D by treating them with low velocity electrons, electrons of high frequency, alternating current of high frequency, x-rays, radium emanations and cathode rays.

Synthetic Oleovitamin D [Viosterol in Oil (Applying only to Activated Ergosterol in Oil)] U.S.P. "is a solution of activated ergosterol, or activated 7-dehydro-cholesterol, in an edible vegetable oil." The viosterol type of a preparation is usually standardized to contain not less than 10,000 U.S.P. Units of vitamin D per gram.

Vitamin D₂ is a white, odorless, crystalline compound that is soluble in fats and in the usual organic solvents, including alcohol. It is insoluble in water.



Vitamin D₂ is slowly oxidized in oils by oxygen of the air, probably via the fat peroxides that are formed. Vitamin A is much less stable under the same conditions.

The structures of vitamin D₂ and tachysterol have been elucidated by Windaus and Thiele³¹ and by Grundmann.³²

Pure vitamin D₂ will protect rats from rickets in daily doses of 0.000,000,015 grams. However, it was soon shown that rat unit for rat unit, vitamin D₂ or irradiated ergosterol was not as effective as cod-liver oil for the chick. Therefore, the vitamin D of cod-liver oil must differ from vitamin D₂. The irradiation of 7-dehydro-cholesterol,³³ when carried out under conditions similar to those used for the irradiation of ergosterol, gave analogous end-products which have been identified as vitamin D₃, lumisterol₃, and tachysterol₃.

Monochromatic light of 296.7 mμ activates 7-dehydrocholesterol to a greater degree than light of any other wave length.³⁴

Vitamin D₃ also occurs in tuna and halibut liver oils, from which it has been prepared³⁵ as a crystalline 3,5-dinitro-

benzoate indistinguishable³⁶ from that obtained by the irradiation of 7-dehydro-cholesterol. One milligram of crystalline vitamin D₃ has the activity of 40,000 I.U.³⁷ and, therefore, has the same activity as vitamin D₂ in rats. Vitamin D₃ is more effective for the chick; however, both vitamins have equal activity for humans.

Vitamin D₃ exhibits stability comparable to that of vitamin D₂.

Epimerization of the C₃OH in vitamin D₂ or D₃ or conversion of C₃OH to a ketone group greatly diminishes the activity but does not completely destroy it. Ethers and esters that cannot be cleaved in the body have no vitamin D activity. Inversion of the hydrogen at C₉ in ergosterol and other 7-dehydrosterols prevents the normal course of irradiation.

Crystalline vitamin D₄ has been obtained from the irradiation products of 22-dihydroergosterol.³⁸ It is one-half to three-fourths as active as vitamin D₂ in rats, but more effective in chicks. The crude product obtained by the irradiation of 7-dehydrositosterol³⁹ is one-fortieth to one-twentieth as active as crude irradiated ergosterol. Irradiated 7-dehydrostigmasterol is one-twenty-fifth to one-four-hundredth as active as irradiated ergosterol,⁴⁰ and irradiated 7-dehydrocampesterol⁴¹ has one-tenth the activity of irradiated 7-dehydrocholesterol. The tachysterols are feebly active, and the loss or partial degradation of the side chain at C₁₇ leads to almost inactive products.

Ergosterol occurs as the characteristic sterol of the cryptogams and in very small amounts in the phanerogams. 7-Dehydrocholesterol has been found in the skins of animals, in birds, molluscs, snails,⁴¹ etc. 7-Dehydrocholesterol is prepared synthetically as are the other 7-dehydrosterols.

Although fish-liver oils serve as excellent sources for vitamin D, they vary greatly in their vitamin D content and in their activity for rats and chicks. Bills⁴² assayed the liver oils from 25 species of fish and found that, although many of these assayed essentially like cod-liver oil, the liver oil of the bluefin tuna is only about one-sixth as potent, rat unit for rat unit, as cod-liver oil. The nonsaponifiable fractions of the oils showed the vitamin D of tuna-liver oil to be one-seventh as potent for chicks,

rat unit for rat unit, as the cod-liver oil vitamin D. Bills states that certain liver oils in this series contain an antirachitic factor which is more effective, rat unit for rat unit, for the chick than cod-liver oil. Apparently the New England and European oils assay like the cod, whereas the California and Oriental species of tuna oils are definitely inferior in relative effectiveness in the chick.

TABLE 53. VITAMIN D CONTENT OF SOME FISH LIVER OILS

SOURCE OF OIL	ANIMAL	POTENCY (I. U./GM.)
Bluefin tuna, liver	<i>Thunnus thynnus</i>	40,000
Swordfish, liver ..	<i>Xiphias gladius</i>	10,000
Yellowfin tuna, liver	<i>Neothunnus macropterus</i> ..	10,000
Black sea-bass, liver	<i>Stereolipis gigas</i>	5,000
Red rockfish, liver	<i>Sebastes ruberrimus</i>	1,500
Chinook salmon, liver	<i>Oncorhynchus tshawytscha</i>	1,300
Halibut, liver	<i>Hippoglossus hippoglossus</i> ..	1,200
Boston mackerel, liver	<i>Scomber scombrus</i>	750
Burbot liver	<i>Lota maculosa</i>	640
Cod, liver	<i>Gadus morrhua</i>	100
Herring, entire body	<i>Clupea harengus</i>	100
Sardine, entire body	<i>Sardinia caerulea</i>	80
Menhaden, entire body	<i>Brevoortia tyrannus</i>	50
Shark, liver		50
Sturgeon, liver ..	<i>Acipenser rubicundus</i>	Nil.

Antirachitic substances have been found in some plants, e.g., the Sargassum weed,⁴³ which grows at shallow depths in the Caribbean, yielded a lipoidal extract that was curative for rickets. A number of edible mushrooms⁴⁴ and corn silages⁴⁵ have shown antirachitic activity.

The exact mode of action of vitamin D is not clearly defined. It does affect the absorption and utilization of calcium and phosphorus. In children and some experimental animals, e.g., dogs, a deficiency of vitamin D without a great distortion of the diet is sufficient to produce rickets. With rats, the

commonly used experimental animal, the calcium and phosphorus of the diet must be restricted or fed in unusual proportions to produce rickets. When the calcium and phosphorus are about equal, rickets cannot be produced in rats. In rats, a diet high in calcium and low in phosphorus, 4:1 to 5:1,* readily produces rickets, curable by the administration of vitamin D. The same is true for low calcium-high phosphorus diets. In cases in which the amounts of calcium and phosphorus were sufficient and the disproportion (2:1 or 1:2) not too great, normal bones were produced and extra vitamin D was not needed. The above is also apparently true for humans. The above factors are not the only ones which play a role in the metabolism of calcium and phosphorus. An excess of acid in the diet causes a depletion via excretion of calcium and phosphorus and leads to rickets. Correct amounts of acidity in the duodenum favor absorption, while alkalinity leads to precipitation and excretion.

Because vitamin D plays a role in the absorption of calcium and phosphorus from the intestinal tract, it follows that the level of these substances in the blood stream would also be affected. When vitamin D is given, the blood serum values tend to become normal, regardless of the type of diet. With rather wide ranges of vitamin D dosage, these values remain normal; however, with massive doses of vitamin D the calcium content of the blood becomes excessive and the phosphate content may be depressed if it is high.

In some unknown manner, vitamin D decreases to a normal level the abnormally high phosphatase content of the blood serum found in rachitic animals and humans. This enzyme is believed to be concerned with the deposition of calcium phosphate in the bones.

Lack of vitamin D in the diet, particularly in infants and children, leads to rickets, which is characterized by defects in the calcification of growing bones. It may be de-

tected by roentgenologic examination of the bones or, in experimental animals, by chemical analysis of the bone ash, by histologic examination⁴⁶ or by other methods.

The changes in the bones in rickets result in those gross manifestations which are recognized clinically⁴⁷ by enlargement of the wrists, knees, and ankles, bowed legs, beading of the ribs, and the rachitic rosary, Harrison's groove and craniotabes.

The administration of vitamin D to a rachitic subject starts calcification at the line of provisional calcification. The first histologic evidence of repair is the presence along the diaphyseal border of degenerated cartilage cells. This effect is visible at the end of 24 hours and is accompanied by extensive vascular penetration within 48 hours. The penetration of blood vessels permits the deposition of the bone-forming salts. There is thus produced the so-called line test[†] for healing. The mass of irregular cartilage cells becomes arranged in short, orderly, parallel columns of a few cells, osteoid material is formed and repair takes place to a remarkable degree. There is no fundamental pathologic condition in the rachitic bone which prevents its calcification. The function of vitamin D is to so alter the body fluids that bone salts may be incorporated into the growing bone. This incorporation (precipitation) can take place when an adequate concentration of Ca, P and CO_3 ions is present.⁴⁸ This complex salt is a dahllite, $n \text{Ca}_3(\text{PO}_4)_2\text{CaX}$, in which n varies between 2 and 3 and X may be CO_3 , OH or F. It may be considered as a solid solution of CaCO_3 in $\text{Ca}_3(\text{PO}_4)_2$. The ratio of one mole of CaCO_3 to two moles of $\text{Ca}_3(\text{PO}_4)_2$ is practically constant for adult bone.

Massive doses[‡] of vitamin D result in a blood level of calcium and phosphorus above normal. This leads to an increased rate of calcification: the structures most affected are the tubules of the kidney, the blood vessels,

* Expressed as percentages in the diet, i.e., 1.2 per cent calcium and 0.25 per cent phosphorus.

† In the assay of vitamin D containing materials using vitamin D depleted rats.

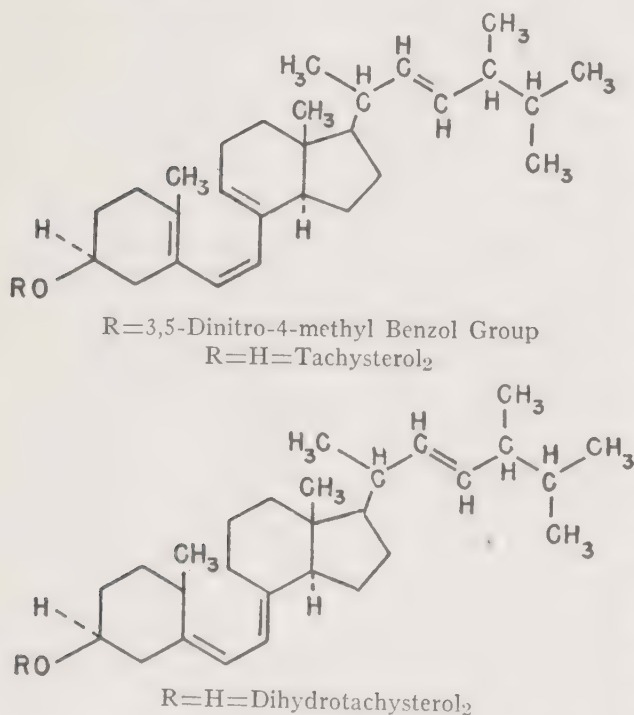
‡ 1,000 times the therapeutic dose.

the heart, the stomach and the bronchi. There is evidence of irritation and degeneration in these tissues and in the liver. The animals under these conditions lose weight rapidly, have intense diarrhea and die in from five to fourteen days. With smaller doses, death is delayed or the animal survives.

The international unit of vitamin D is equivalent to 0.025 micrograms of crystalline vitamin D₂.

The average daily requirement of vitamin D is from 400 to 800 I. U.

Dihydrotachysterol₂ (A.T. 10, Hytakerol). Reduction by sodium and alcohol of the 3,5-dinitro-4-methylbenzoic acid ester of tachysterol₂ followed by saponification leads to the production of dihydrotachysterol,⁴⁹ which can be obtained in a crystalline form.



Dihydrotachysterol is a white, crystalline compound that is soluble in oils and the usual organic solvents. It melts at 125-127° C. and shows absorption maxima at 242, 251 and 261 mμ.

Dihydrotachysterol has slight antirachitic activity.⁵⁰ It causes an increase of the calcium concentration in the blood, an

effect for which tachysterol is only one-tenth as active.

Dihydrotachysterol (A.T. 10, meaning antitetanus) is used in infantile tetany⁵¹ and in postoperative (hypoparathyroid) tetany, in which conditions it increases the calcium content of the blood serum through absorption from the gut. Both vitamin D₂ and dihydrotachysterol are of equal value in hypoparathyroidism. In parathyroid tetany, an initial dose of 2 to 8 milligrams of dihydrotachysterol or 10 to 40 milligrams of vitamin D₂ (400,000 to 1,600,000 I.U.) is followed by a maintenance dose of 0.6 to 1.0 milligrams of dihydrotachysterol or 3 to 5 milligrams of vitamin D₂.

VITAMIN C

Ascorbic Acid (Vitamin C) U.S.P. (Cevitamic Acid, Cebione). The disease scurvy, which is now known as a condition due to a deficiency of ascorbic acid in the diet, has considerable historical significance.⁵² For example, in the war between Sweden and Russia (most likely the march of Charles XII into the Ukraine in the winter of 1708—1709) almost all of the soldiers of the Swedish army became incapacitated by scurvy. But further progress of the disease was stopped by a tea prepared from pine needles. The Iroquois Indians cured Jacques Cartier's men in the winter of 1535—1536 in Quebec by giving them a tea brewed from an evergreen tree. Many of Champlain's men died of scurvy when they wintered near the same place in 1608—1609. During the long siege of Leningrad, lack of vitamin C made itself particularly felt, and a decoction made from pine needles played an important role in the prevention of scurvy. It is somewhat common knowledge that sailors on long voyages at sea were subject to the ravages of scurvy. The British used supplies of limes to prevent this, and the sailors often were referred to as limeys.

Holst and Frolich,⁵³ in 1907, first demon-

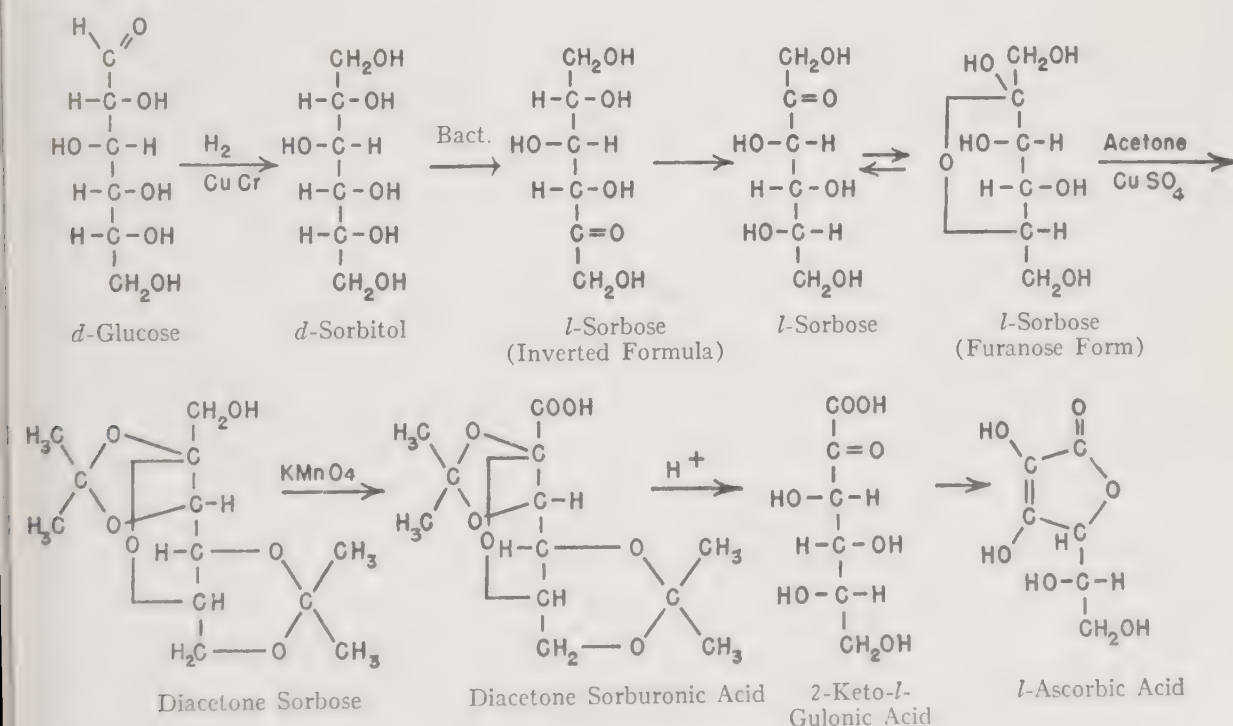
strated that scurvy could be produced in guinea pigs. A comparable condition cannot be produced in rats.

Although King and Waugh⁵⁴ (1932) isolated crystalline vitamin C from lemon juice and showed it to be the antiscorbutic factor of lemon juice, Szent-Gyorgyi⁵⁵ had isolated the same substance from peppers in 1928 in connection with his biologic oxidation-reduction studies. At the time he failed to recognize its vitamin properties and reported it as a hexuronic acid because some of its properties resembled those of sugar acids. Hirst, *et al.*,⁵⁶ suggested that the correct formula should be one of a series of possible tautomeric isomers and offered basic proof that the formula now generally accepted is correct. The first synthesis of *l*-ascorbic acid (vitamin C) was announced almost simultaneously by Haworth and by Reichstein⁵⁷ in 1933. Since that time ascorbic acid has been synthesized in a number of different ways, the following of which has proved commercially feasible.⁵⁸

and uncertain. It is, therefore, not prepared in a crystalline state from natural sources; however, concentrates have been and are prepared for human use.

Vitamin C is distributed very widely in the active tissues of higher plants. It is formed rapidly in germinating seeds and apparently reaches a high concentration in rapidly growing stem or root tips, green leaves and seeds. Almost all fresh fruits and tubers contain significant amounts of this vitamin. This is especially true of the citrus fruits, peppers, paprikas, tomatoes, rose hips, blackberries, green English walnuts, West Indian cherries,⁵⁹ etc. Gladioli⁶⁰ contain 10 per cent ascorbic acid dry weight, and *Primula officinalis* contains 6 per cent dry weight. The leaves or flowers of a number of inedible ornamental plants are very rich in vitamin C.⁶⁰

Vitamin C is found in all parts of the body, including the blood stream. It occurs in greater concentrations in the adrenal

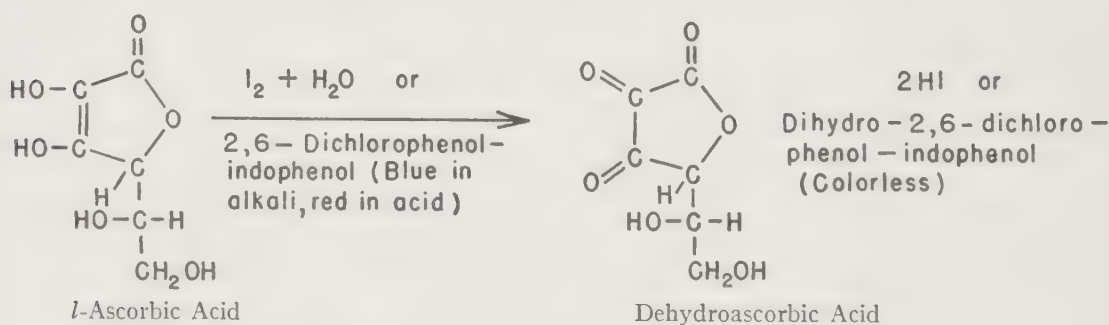


Although ascorbic acid occurs in relatively large quantities in some plants, fruits, etc., its isolation is tedious, difficult

glands and in the lenses of the eyes than it does in any other part of the body.

Ascorbic acid occurs as white or slightly yellow crystals or powder. It is odorless and on exposure to light it gradually darkens. One gram of ascorbic acid dissolves in about 3 cc. of water and in about 30 cc. of alcohol. A one per cent aqueous solution has a pH of 2.7.

Vitamin C was given the name ascorbic acid⁶¹ because it exhibited acid properties and would cure scurvy. The enolic groups impart acidity⁶² to the molecule so that the preparation of salts* is possible; these can be regenerated by treatment with a stronger acid, i.e., hydrochloric acid. Vitamin C shows marked reducing properties but no color with Schiff's reagent. It is quantitatively reversibly oxidized in aqueous solution by iodine or by 2,6-dichlorophenol-indophenol. The iodine reaction is employed in the official assay, whereas the dye is used in the estimation of ascorbic acid in natural extracts and ascorbic acid tablets.



Ascorbic acid is reasonably stable in the dry state. In solution it is slowly oxidized under acid conditions but is rapidly oxidized in alkaline conditions. The above oxidations are catalyzed by metals such as iron, copper, manganese, etc.

Ascorbic acid exhibits no mutarotation, it gives a color with ferric chloride and with basic lead acetate yields a precipitate that can be decomposed with hydrogen sulfide. Ascorbic acid can be sterilized in the presence of phenol when heated in an autoclave for short periods of time.

Man, the other primates, the guinea pig and a few micro-organisms are not able to

synthesize ascorbic acid. Although other animals and plants also need ascorbic acid, they are able to synthesize it.

Vitamin C is a specific for the prevention and cure of scurvy. This deficiency disease occurs in humans, monkeys and guinea pigs. Rats do not need ascorbic acid in their diets. The symptoms of this deficiency disease are loss of weight; swollen, soft, spongy or ulcerated gums; loose carious teeth; hemorrhages; necrosis of the bones; swollen joints; edema; hardening of the skin and often perifollicular or petechial hemorrhages; sometimes bloody conjunctiva and occasionally, anemia. The tendency to bleed, capillary fragility, accompanied by ready injury to the vascular system is a general one. The joints become painful.

In the absence of vitamin C there is a loss in the development and maintenance of intercellular substances. This involves the collagen of all fibrous tissues and of all non-

epithelial cement substances such as intracellular material of the capillary wall, cartilage, dentin and bone matrices. Because vitamin C is readily oxidized and reduced, it is possible that its function in the development and maintenance of intercellular substances in the above tissues may be a respiratory one. In glandular tissues, there seems to be some correlation between the high concentration of ascorbic acid and the general rate of metabolism. This is analogous to the correlation that exists in plants. The fact that the amount of ascorbic acid is larger in young and actively growing tissues than it is in older and less active tissues seems to

* See Sodium Ascorbate Injection—U.S.P.

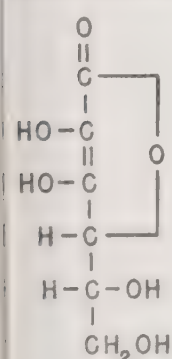
indicate that it has some respiratory influence. A corticometric principle that contains ascorbic acid in its molecule has been isolated.

The amino acids phenyl alanine and tyrosine are not completely metabolized in vitamin C deficient individuals. Under these conditions they are only partly metabolized and are excreted in the urine as homogenetic, *p*-hydroxyphenylpyruvic and hydroxyphenyllactic acids. An increase in the amounts of phenylalanine and tryosine ingested is accompanied by an increased need for vitamin C. Vitamin C in adequate amounts delays the oxidation of epinephrine by the body.

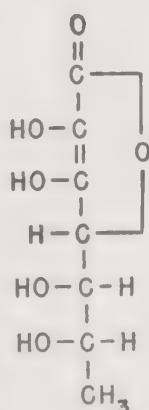
Although ascorbic acid is the only compound found in nature that has vitamin C properties, a large number of closely related compounds have been prepared and tested for their activities. From these studies it can be concluded that in addition to the two enolic groups, the *d*-configuration₆₃ of the fourth carbon atom (essential configuration for dextrorotatory lactone) and the *l*-configurations of the fifth carbon atom are necessary for maximum antiscorbutic activity. The terminal primary alcohol group also contributes to the activity, because 6-deoxy-*l*-ascorbic acid is one-third as active as *l*-ascorbic acid. The following compounds exhibit some activity.

possesses practically no antiscorbutic properties, and, therefore, no regeneration of 2,3-diketo-*l*-gulonic acid appears likely in the animal body. The simultaneous loss of reducing and antiscorbutic properties when the lactone ring is opened further suggests that the reducing action of ascorbic acid is in some way associated with its biologic function.

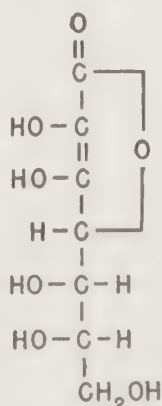
Vitamin C is continuously excreted in the urine, and ingestion of amounts above those required to saturate the tissues will also be excreted. This provides a measure of the vitamin C reserve. The titration of the ascorbic acid in the urine with indophenol, after a standard dose of vitamin C has been given, provides a direct, rapid and simple method of evaluating the condition of the body tissues in terms of vitamin C reserve. The vitamin C level can also be estimated by measuring capillary strength or by direct titration of ascorbic acid in the blood or spinal fluid. Others suggest that low plasma ascorbic acid levels indicate only the degree of saturation and are a poor index of deficiency. Patients placed upon a diet deficient in vitamin C exhibited the following: (1) 10 days, plasma fell to a low level; (2) 30 days, plasma level was zero; (3) 13 weeks, first clinical evidence of scurvy; (4) 132 days, hyper-



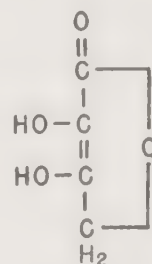
Isovitamin C
(1/20 to 1/50 Activity)



l-Ramno-ascorbic Acid
(1/5 activity)



l-Glucoascorbic Acid
(1/40 activity)



2,3-Ene-diol-4-lactone
(slightly active)

d-Ascorbic, *d*-gluco-ascorbic and *d*-galactoascorbic acids are inactive in guinea pigs.⁶⁴ 2-Keto-*l*-gulonic acid when fed to guinea pigs

keratotic papules developed; (5) at 141 days, wounds failed to heal, and (6) 162

days, perifollicular hemorrhages of scurvy developed, and the ascorbic acid value of the white coil platelets fell to zero. Loss of weight occurred accompanied by a lowered blood pressure.

Large doses of vitamin C have been of distinct value in the treatment of hay fever, for the relief of heat cramps and heat prostration in workers in an extremely hot environment and as a detoxifying agent for arsenicals. Ascorbic acid is nontoxic even in massive doses.

The daily human requirement is usually the amount of ascorbic acid needed to maintain at least 1 milligram per cent in the plasma. This amount may vary from 30 to 100 milligrams. It can be administered orally, intramuscularly or intravenously.

The U.S.P. and the international unit are equivalent to 0.05 milligrams of pure ascorbic acid.

The average dose is to be determined by the physician according to the needs of the patient.

Sodium Ascorbate Injection U.S.P. The enolic groups of ascorbic acid are sufficiently acidic so that the sodium salt can be prepared. This salt is stable in the ab-

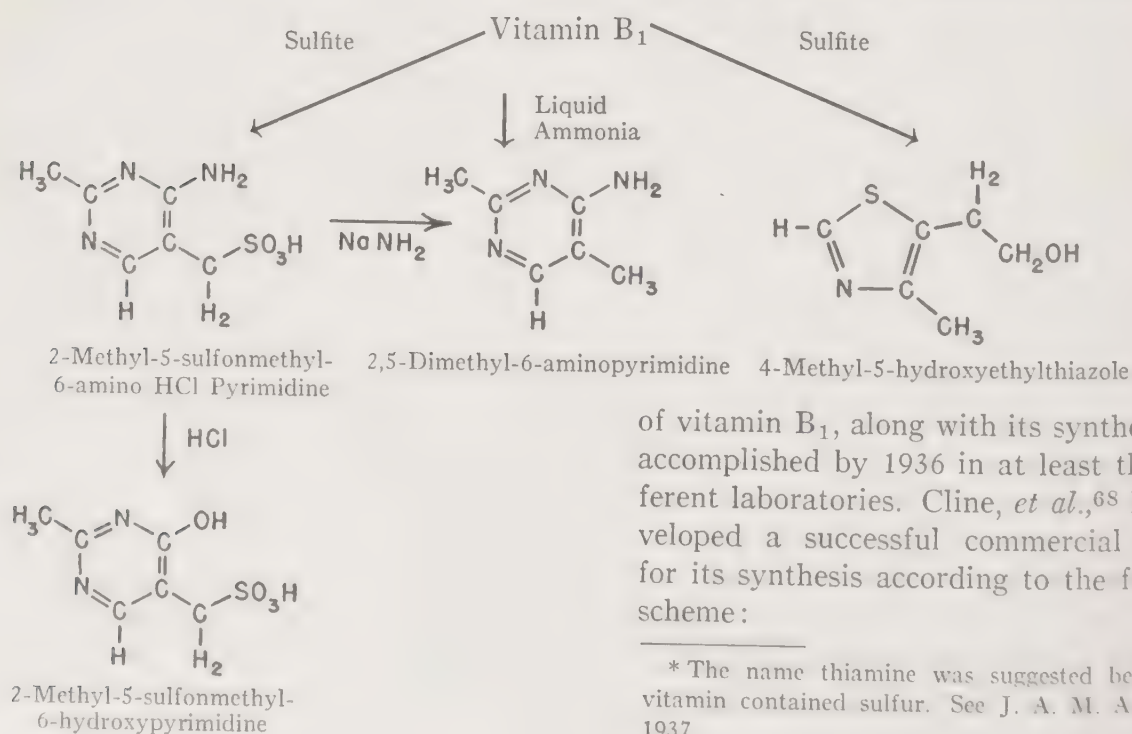
sence of oxygen of the air. It can be used for intravenous injection, whereas ascorbic acid is too acidic for this purpose. Sodium ascorbate can be prepared from sterile ascorbic acid and sterile sodium bicarbonate; however, such preparations should be used immediately to prevent the degradation of ascorbic acid.

THIAMINE HYDROCHLORIDE

Thiamine* Hydrochloride (Thiamin Chloride, Vitamin B₁ Hydrochloride, Vitamin B₁, Aneurine Hydrochloride) U.S.P. Thiamine hydrochloride, the first water-soluble vitamin to be obtained in a crystalline form, was isolated from rice bran by Jansen and Donath⁶⁵ in 1926. They reported its formula to be C₆H₁₀ON₂. Later, in 1932, a more nearly correct formula, C₁₂H₁₈ON₄SCl₂, was given by Windaus *et al.*⁶⁶ Several laboratories have contributed to the elucidation of its structural formula. Williams, *et al.*,⁶⁷ working with very large quantities, were able to isolate sufficient quantities of thiamine hydrochloride for degradative studies.

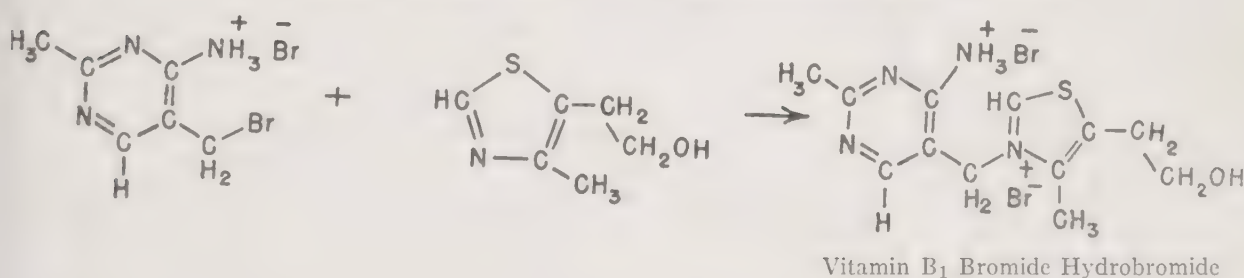
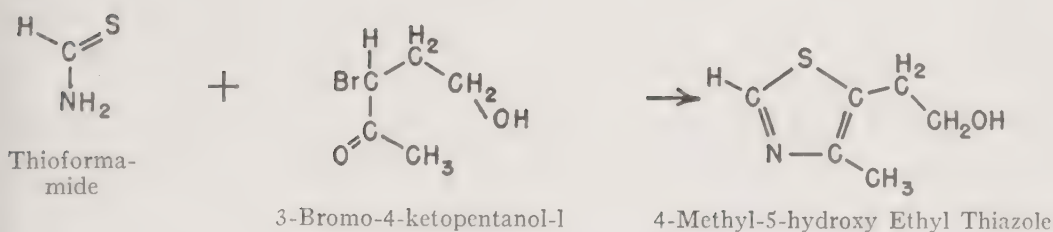
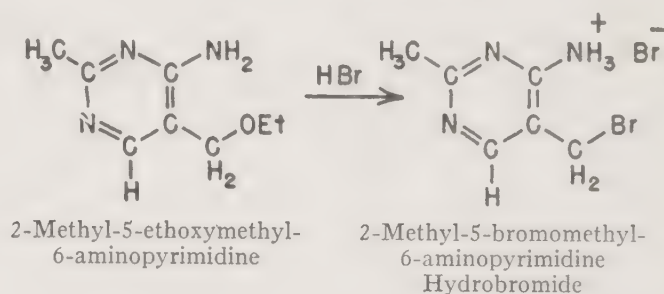
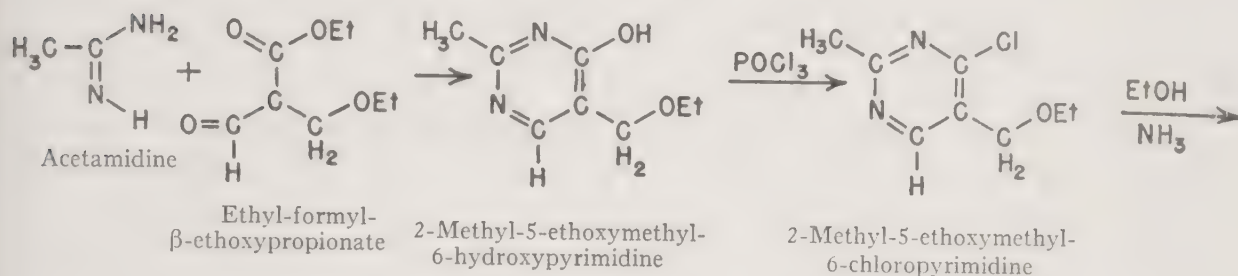
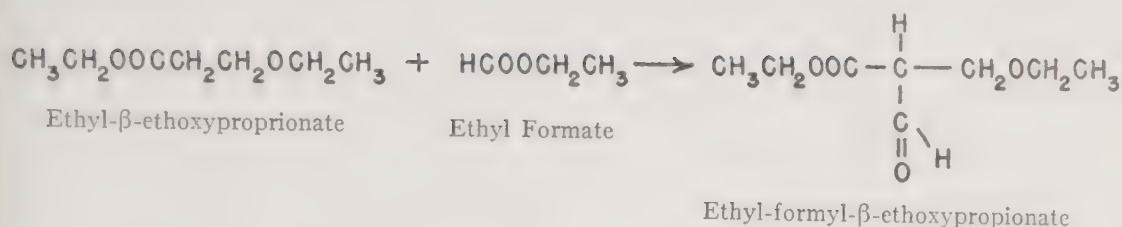
The following scheme indicates the products obtained from different methods of cleavage.

The complete elucidation of the structure



of vitamin B₁, along with its synthesis, was accomplished by 1936 in at least three different laboratories. Cline, *et al.*,⁶⁸ have developed a successful commercial method for its synthesis according to the following scheme:

* The name thiamine was suggested because this vitamin contained sulfur. See J. A. M. A. 109:952, 1937.



Many natural foods have been shown to contain moderate quantities of vitamin B₁. The germ of cereals, brans, egg yolks, yeast extracts, peas, beans and nuts are good sources of B₁. It is too costly to isolate the crystalline vitamin on a commercial scale, and all vitamin B₁ so marketed is prepared synthetically. However, concentrates from rice, bran, yeast, etc. that contain other water-soluble vitamins in a concen-

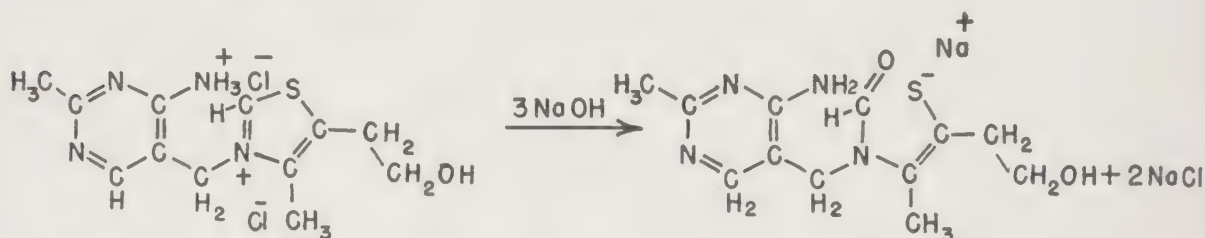
trated form in addition to the vitamin B₁ are marketed.

Thiamine hydrochloride occurs as small, white crystals or as a crystalline powder; it has a slight, characteristic yeastlike odor. The anhydrous product, when exposed to air, will rapidly absorb about 4 per cent water. One gram is soluble in 1 cc. of water and in about 100 cc. of alcohol. An aqueous solution, 1 in 20, has a pH of 3. It is

soluble in glycerin. Aqueous solutions are acid to litmus.

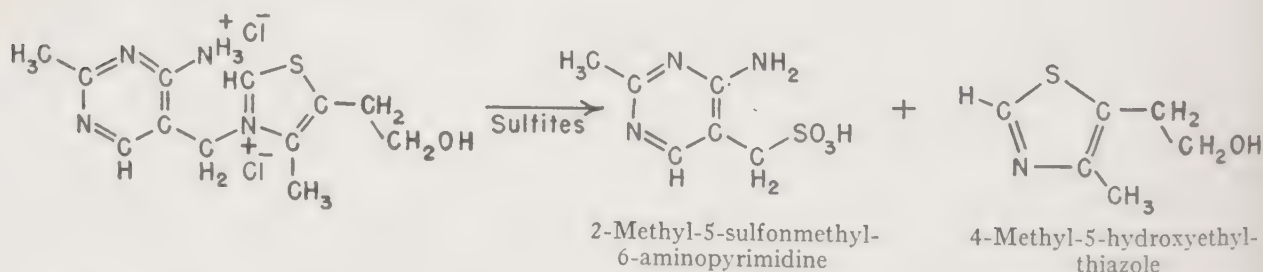
Thiamine hydrochloride, because it contains a free amino group, a quaternary amino group and a pyrimidine ring, gives a positive test with some of the alkaloidal reagent test solutions, such as mercuric potassium iodide, trinitrophenol, iodine and bichloride of mercury.

Thiamine hydrochloride is sensitive toward alkali.⁶⁹ The addition of three moles of sodium hydroxide per mole of thiamine hydrochloride reacts as follows:



It is generally agreed that the stability of thiamine hydrochloride in aqueous solutions decreases as the pH is increased above 5. The following substances, which are capable of increasing the pH of thiamin preparations above the danger point, include sodium bicarbonate, sodium salicylate, sodium barbiturates, sodium citrate, aminophyllin, sodium sulfa drugs, etc.

At a pH of 5 to 6, thiamine is readily cleaved by sulfites as follows:



Thiamine⁷⁰ hydrochloride is readily oxidized by air,⁷¹ hydrogen peroxide, permanganate or alkaline potassium ferricyanide⁷² to give thiochrome, which exhibits a vivid blue florescence and furnishes the basis for the quantitative colorimetric assay of this vitamin. (See the equation at the

top of page 509 for this reaction.) This assay is official in the U.S.P.

The amino group in thiamine will readily react with aldehydes to form Schiff bases, and these compounds are inactive. The amino group apparently labilizes the pyrimidine ring so that it undergoes a coupling reaction; thus, highly colored compounds can be made, and have been used as a basis of colorimetric assays. Thiamine is quite stable in acid media, and cleavage

does not occur even at a pH of 4 or less when heated at 120° C. for twenty minutes. In the dry state it can be heated at 100° C. for 24 hours without diminishing its potency.

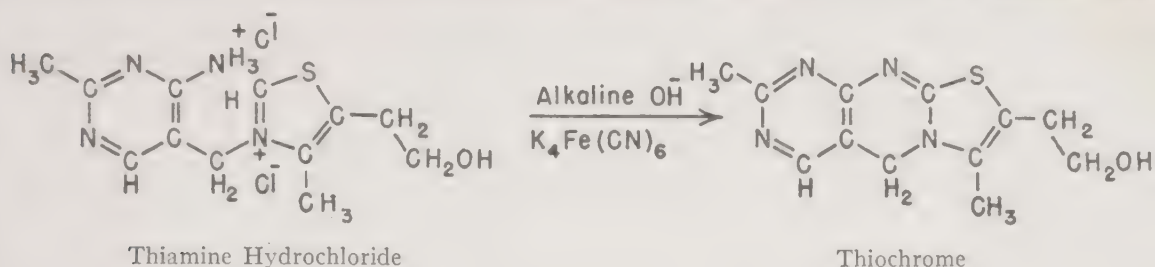
Many methods of assay⁷³ have been developed for thiamine. These can be grouped as follows.

BIOLOGIC METHODS

ANIMALS

1. Prevention of polyneuritis in pigeons, fowls, chicks or rice birds.
2. Cure of polyneuritis in pigeons* or mice.

* Most useful of the biologic assays.



3. Rate of growth of rats* or mice.
4. Weight maintenance of rats and pigeons.
5. Restoration of weight and appetite of pigeons, rats* or dogs.
6. Cure of particular symptoms such as bradycardia in rats or pigeons, and cure of nystagmus in rats.

PLANTS AND MICRO-ORGANISMS

1. Yeast growth and fermentation.
2. Growth of cocci.
3. Growth of *Phycomyces Blakesleeanus*.

CHEMICAL METHODS

1. Conversion to thiochrome for colorimetric assay.†
2. Azo tests whereby a red color is produced by adding diazotized sulfanilic acid to a solution containing thiamine in the presence of formaldehyde.
3. Coupling with diazotized *p*-aminoacetanilide or *p*-amino acetophenones to produce a red dye.

A large number of compounds⁷⁴ related in structure to vitamin B₁ have been prepared and tested for their activity. The following groups have been found necessary for activity.⁷⁵

1. The amino group on the pyrimidine ring.
2. A 5-β-hydroxyethyl group on the thiazole ring.
3. A hydrogen in position 2 on the thiazole ring.

4. A methylene bridge between the thiazole and the pyrimidine rings.

Vitamin B₁ can be modified as follows and still retain activity in certain biologic tests, though the activity is of a much lower order.

1. A hydrogen atom of the amino group on the pyrimidine ring can be replaced by an alkyl group.
2. The methyl group at position 2 in the pyrimidine ring can be replaced by an ethyl group.
3. The methyl group at position 2 in the pyrimidine ring can be shifted to the 4 position.
4. The hydroxyl group in the side chain at position 5 of the thiazole ring can be replaced by bromine or chlorine.

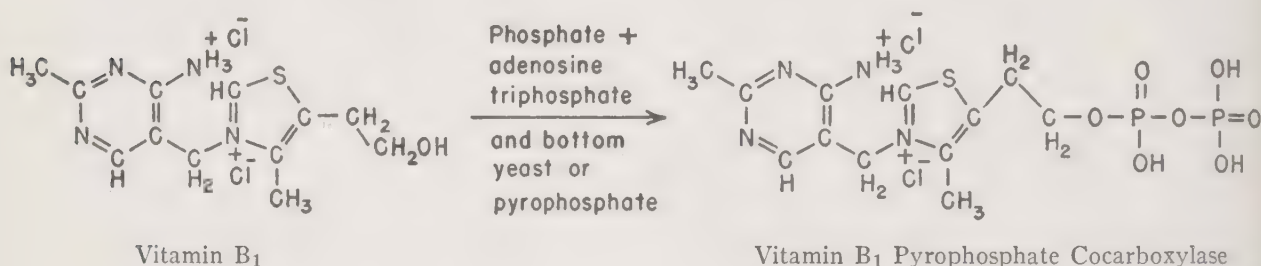
It is interesting to note that animals can use only the fully synthesized vitamin, while plants and some micro-organisms can utilize the pyrimidine or thiazole portion alone, whereas, others require both of these fragments.

Potent antithiamine compounds have been prepared by a modification of a portion of the vitamin B₁ molecule. Thus, pyriethamine⁷⁶ [2-methyl-4-amino-5-pyrimidylmethyl - (2 - methyl - 3 - hydroxyethyl)-pyridinium bromide], for example, inhibits the growth of fungi, and when given to mice, will induce signs of vitamin B₁ deficiency. This condition can be prevented or alleviated by administering vitamin B₁ in the ratio of one mole to 40 moles of pyriethamine.

* Most useful of the biologic assays.

† U.S.P. Method of Assay.

Vitamin B₁ occurs in the free state in plants. In yeast, some of the vitamin B₁ is present as the pyrophosphate known as cocarboxylase. In mammalian tissue, all of the vitamin B₁ occurs as the pyrophosphate. Cocarboxylase has been isolated in a crystalline form⁷⁷ and has also been synthesized from vitamin B₁ by both the use of enzymes⁷⁸ and by chemical (in vitro) methods.⁷⁹



In yeast, cocarboxylase, together with carboxylase, decarboxylates pyruvic acid to yield acetaldehyde and carbon dioxide. Because abnormally large amounts of pyruvic acid have been found in the blood of experimental animals suffering from beriberi, whereas these animals cured by vitamin B₁ have a normal concentration, it is thought that cocarboxylase in mammals also plays a role in the metabolism of pyruvic acid. The exact role that cocarboxylase plays in the metabolism of pyruvic acid is not clearly understood, although decarboxylation is a very favorable possibility. Vitamin B₁ may also play a role in the decarboxylation of 2-ketophosphohexonate, oxalosuccinate and α-ketoglutarate. Cocarboxylase apparently does not act as a hydrogen carrier in biologic systems because the catalytically reduced cocarboxylase is biologically inactive.

Because vitamin B₁ plays a role in the metabolism of carbohydrates, and also possibly of amino acids and fats, the source of energy in each cell is affected. Those tissues and organs which utilize the greatest amounts of carbohydrates will be af-

ected the most. The condition known as beriberi, in the adult, is characterized by multiple neuritis, muscular atrophy, cardiovascular changes, serous effusions and generalized edema. These manifestations vary so greatly in number and severity and order of appearance from one patient to another that beriberi has come to be classified into several types, i.e., (1) dry beri-

beri; (2) wet beriberi; (3) cardiac, pernicious or acute beriberi and (4) mixed beriberi.⁸⁰

The signs and symptoms of clinical beriberi are loss of strength, fatigue, headache, insomnia, nervousness, dizziness, dyspnea, loss of appetite, dyspepsia, tachycardia and tenderness of the calf muscles.

The following systems are affected by a marked deficiency of vitamin B₁.

1. Skin and other epithelial tissues—atrophy, scaling, dermatitis, pigmentation, ulceration and cornification.

2. Nervous system—a neuritis accompanied by pain, paresthesia, weakness and paralysis; degeneration of the spinal cord and mental disturbances.

3. Alimentary tract—anorexia, stomatitis, glossitis, atrophy of the tongue, achlorhydria, diarrhea, loss of tone of gastrointestinal tract and ulceration of the intestine.

4. Hematopoietic system—macrocytic, microcytic and hypochromic anemias.

5. Cardiovascular system—hemorrhage, easy bruising, edema, nutritional heart disease and enlargement of the heart.

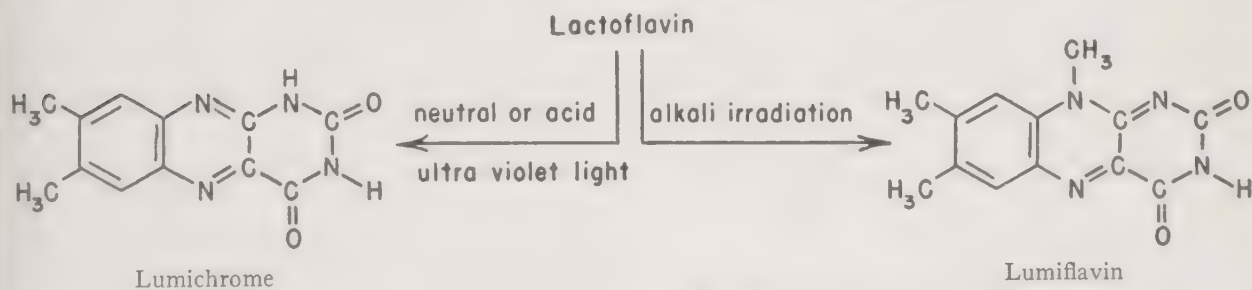
According to the U.S.P., the dosage of thiamine hydrochloride should be determined by the physician. A suggested minimal daily requirement for man is approximately 0.5 mg. per 1,000 calories, and the optimal requirement probably lies between 0.5 and 1.0 mg. per 1,000 calories.

RIBOFLAVIN

Riboflavin (Lactoflavin, Vitamin B₂, Vitamin G.) U.S.P. in the years 1932 and 1933 riboflavin was isolated from milk and egg white and was called lactoflavin and oboflavin by Ellinger and Koschra,⁸¹ and by Kuhn *et al.*⁸² It was isolated as a coenzyme enzyme-complex, from yeast, by Warburg and Christian,⁸³ who designated this complex as "yellow oxidation ferment." Szent-Gyorgy and Banga⁸⁴ and Bleyer and Kallman,⁸⁵ in the same years, no doubt also isolated an enzyme-complex containing riboflavin. These isolations were accomplished in connection with studies in the field of respiratory-

essary for the growth of young rats. The presence of a substance with the same activity was demonstrated by researchers to be present in germinating wheat, egg yolk, yeast, liver, in crude casein and widely distributed in the plant and animal kingdom. Attempts to obtain this growth factor for rats in a pure form resulted only in the preparation of very active fractions.

Kuhn *et al.*,⁸⁸ in 1933, demonstrated that lactoflavin could be substituted in diets deficient in the rat-growth factor to obtain normal growth and, thus, they established its vitamin nature and synonymity with vitamin B₂. Kuhn⁸⁹ showed that the irradiation of lactoflavin in neutral and alkaline media yielded chloroform-soluble, colored fragments, i.e., lumichrome and lumiflavin, from which a sugarlike side chain was lost. These studies, together with other data,⁹⁰ furnished clues that led to the synthesis of riboflavin. The chloroform-soluble fragments furnish a basis for the colorimetric estimation of riboflavin.

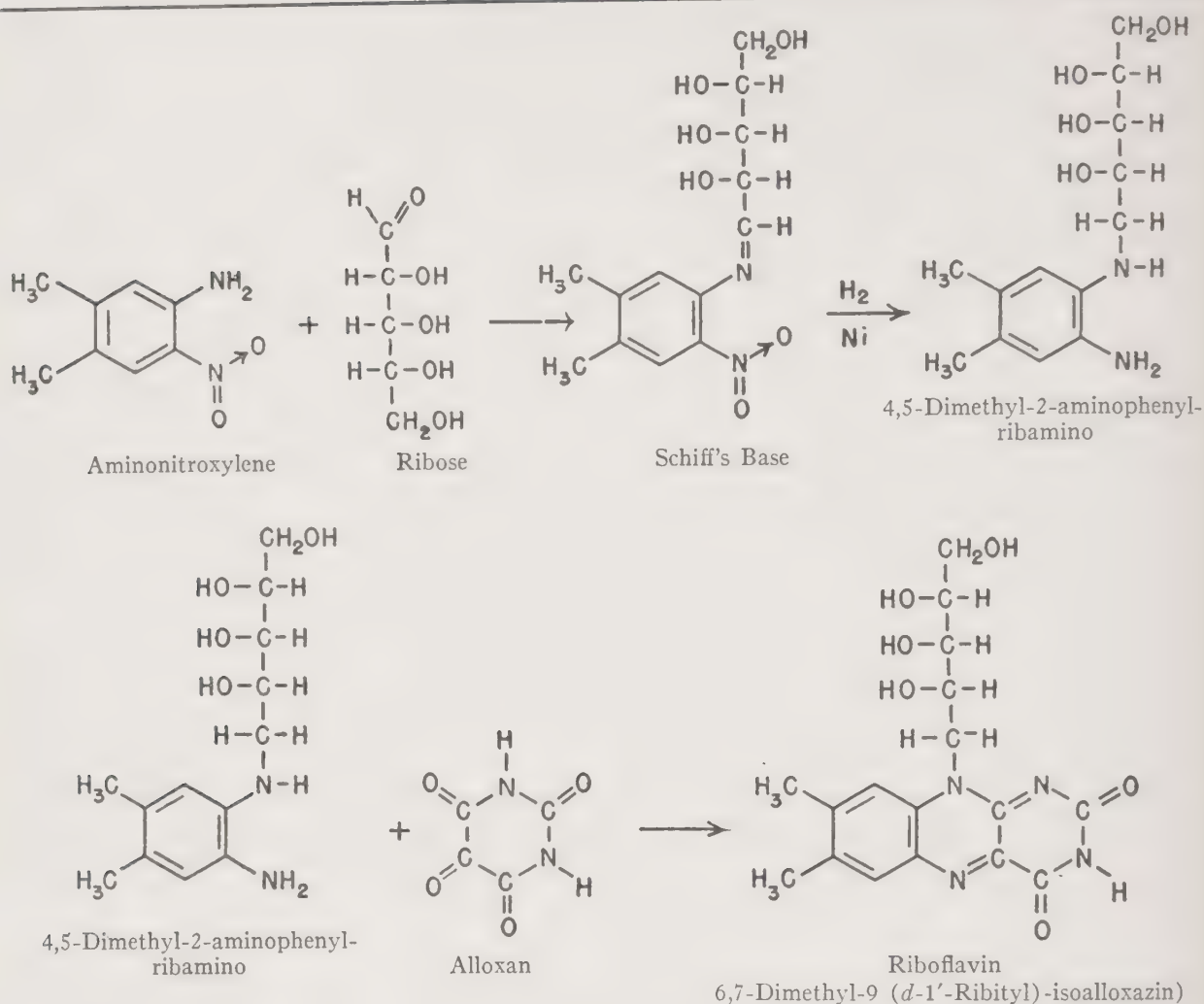


enzyme systems that involved biologic oxidations and reductions. Crystalline flavins were isolated from plant and animal sources and were designated as hepaflavin from liver and verdoflavin from grass. Flavins were also isolated from dandelions, malt and shellfish eyes. All these flavins appeared to be identical with riboflavin.

Although the successful isolation of crystalline riboflavin was not accomplished until 1932 and 1933, interest in this pigment dates back to about 1881 in connection with the color⁸⁶ in the whey of milk. Osborne and Mendel,⁸⁷ in 1913, showed that a water-soluble factor was present in milk that was nec-

Riboflavin has been synthesized by a number of methods, some of which are used commercially.⁹⁰ (See the equations at the top of page 512.)

In the synthesis on page 512 the rare sugar ribose is obtained from yeast nucleic acids. Ribose can be synthesized by starting with galacturonic acid, which is readily prepared from pectin. However, it is very expensive and knowledge in sugar chemistry has permitted the production of *d*-ribonic acid by epimerization of *d*-arabonic acid, which in turn can be readily prepared from *d*-glucose. The above ribonic acid can be used in a number of ways in the synthesis of riboflavin. The alloxan is obtained by the ox-



idation of barbituric acid or uric acid.

Riboflavin is found widely distributed in nature. The best sources are yeast, rice polishings, wheat germ, turnip greens, liver, milk and kidneys. Excellent sources are lean beef, eggs, spinach, beet greens, oysters, veal, etc.

Riboflavin is a yellow to orange-yellow, crystalline powder with a slight odor. One gram of riboflavin dissolves in 10,000 cc. of water but it is more soluble in an isotonic solution of sodium chloride. A saturated aqueous solution has a pH of 6. It is less soluble in alcohol and insoluble in ether or chloroform. Benzyl alcohol (3 per cent), gentisic acid (3 per cent), urea in varying amounts and niacin amide are used to solubilize riboflavin when relatively high concentrations of

this factor are needed for parenteral solutions.

When dry, riboflavin is not appreciably affected by diffused light; however, as previously mentioned, it deteriorates in solution in the presence of light, and this deterioration is very rapid in the presence of alkalis. This deterioration can be retarded by buffering on the acid side.

A large number of flavins have been synthesized by varying the substitution in the benzene ring and the nature of the polyhydroxy side chain at position 9. The following flavins have about one-half of the biologic activity of riboflavin itself: (1) 6-methyl-9-(d-1'-ribityl)-isoalloxazine, (2) 7-methyl-9-(d-1'-ribityl)-isoalloxazine, (3) 6-ethyl-7-methyl-9-(d-1'-ribityl)-isoalloxazine.

The antipode of riboflavin, 6,7-dimethyl-9-(1-l'-ribityl)-isoalloxazine, has one-third the biologic activity of riboflavin.

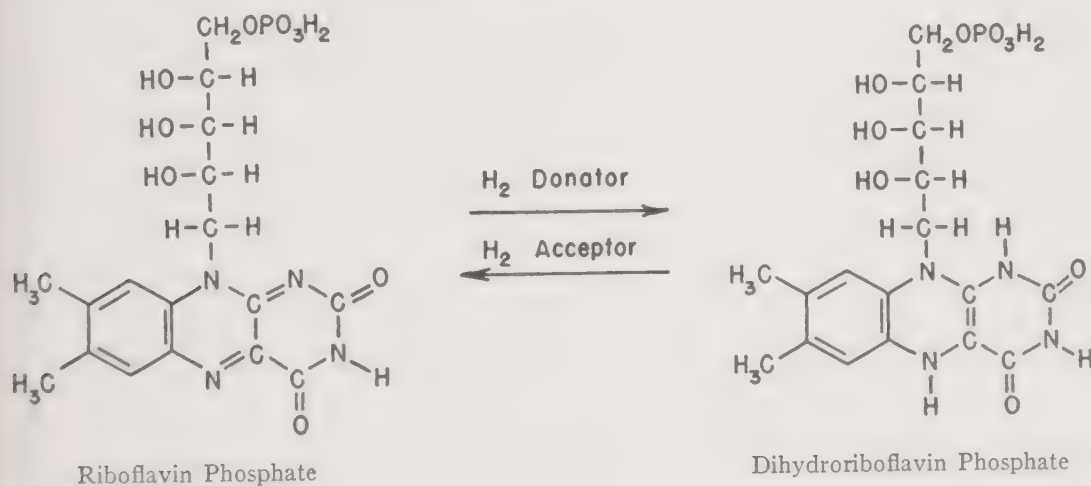
Some flavins do not produce a permanent growth in rats; in fact, after a temporary increase in weight, growth is arrested, and the animal finally dies. Examples of these flavins are: (1) 6,7-dimethyl-9-(1-l'-arabityl)-isoalloxazine, (2) 6,7-dimethyl-9-(*d*-l'-arabityl)-isoalloxazine, (3) 7-ethyl-9-(*d*-l'-ribityl)-isoalloxazine.

Riboflavin has been shown to exist as the phosphate in a coenzyme in combination with a number of enzymes, as enzyme-coenzyme complexes that function in a number of biologic oxidation-reduction systems. It is also present as the active component of the coenzyme of the *d*-amino acid oxidase which is alloxazine adeninedinucleotide, composed of riboflavin, pyrophosphoric acid, *d*-ribose and adenine. The riboflavin portion of the enzyme-coenzyme complex is thought to act as a hydrogen transporting agent, oxygen, cytochromes, etc., being the acceptors.

also act as hydrogen donators in the presence of the appropriate enzymes (oxidases). The hydrogen acceptor in many cases is the cytochrome system, although oxygen and certain other substrates may also be effective.

A deficiency of riboflavin causes a cessation of growth in rats, together with the following symptoms: opthalmia, dermatitis, falling hair, incrustations of the skin, ulceration of the corners of the mouth and inflammation of the gums.

A deficiency of riboflavin in humans is characterized by cheilosis, seborrheic accumulations in the nasolabial folds, a glossitis (tongue a purplish red or magenta color, whereas, in nicotinic acid deficiency it is a fiery red) and the papillae on the tongue appear flattened or mushroom-shaped. Ocular symptoms are characterized by itching, burning and a sensation of roughness, mild or severe photophobia with dimness of vision in poor light and partial blindness (less common), corneal opacity, congestion



The hydrogen donators may be coenzymes I and II or other suitable substrates. They are reduced in the presence of certain dehydrogenases and suitable substrates, such as alcohol, acetaldehyde, glucose, etc. Riboflavin phosphate may accept hydrogen from α -ketoglutarate, fumarate and pyruvate in the presence of certain enzymes (dehydrogenases). *d*-Amino acids and xanthine may

of the vessels of the bulbar conjunctiva with marked circum corneal injection and progressive vascularization of the cornea (appears as ariboflavinosis is allowed to continue). The peripheral nerves and posterior columns of the spinal cord show myelin degeneration. Riboflavin appears to play some role in blood formation.

It is believed by some investigators that the average American diet is deficient in riboflavin as well as in vitamin B₁.

The U.S.P. states that the dose of riboflavin should be determined by the physician.

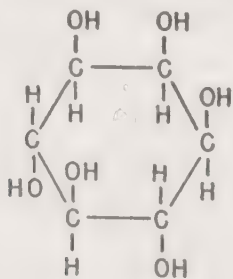
The Sherman unit for riboflavin is the daily dose of material containing this dietary supplement which will induce a gain of 3 grams in rats per week for a period of five weeks. This unit is equal to 2.5 micrograms of crystalline riboflavin. The daily requirement ranges from 0.5 mg. for infants to 3 mg. for adults.

INOSITOL

Inositol (Mouse Anti-lopecia Factor). Eastcott,⁹¹ in 1928, showed that bios I was the well-known, naturally occurring, optically inactive inositol. In 1941, Woolley⁹² showed that mice maintained on an inositol deficient diet ceased growing, lost their hair and finally developed a severe dermatitis. In rats, a denudation about the eyes called "spectacle eye" takes place in the absence of inositol in the diet. These symptoms also are accompanied by the development of a special type of fatty liver containing large amounts of cholesterol.

Inositol is prepared from natural sources such as corn steep liquors and is available in limited commercial quantities. It is a white crystalline powder and is soluble in water and dilute alcohol. It is insoluble in absolute alcohol, the usual organic solvents and in fixed oils. It is stable under normal storage conditions.

i-Inositol is one of nine different cis-trans isomers of hexahydroxycyclohexane and is usually assigned the following configuration.



Inositol has been found in most plants and animal tissues. It has been isolated from cereal grains, other plant parts, eggs,

blood, milk, liver, brain, kidney, heart muscle, etc. The concentration of inositol in leaves reaches a maximum shortly before the time that the fruit ripens. Good sources of this factor are fruits, especially citrus fruits,⁹³ and cereal grains. Large amounts of inositol are found in certain yeasts and molds.⁹⁴

Inositol occurs free and combined in nature. In plants, it is chiefly present as the well-known phytic acid which is inositol hexaphosphate. It is also present in the phosphatide fraction of soy bean as a glycoside.⁹⁵ In animals, much of it occurs free and some combined as the phosphate, possibly with a proteinlike substance.

The mode of action of i-inositol is not known, and its optically active isomers are physiologically inactive. Phytin (calcium-magnesium salt of inositol hexaphosphate), inositol hexaacetate, cephalin⁹⁶ and methyl-inositol (Mytilitol) are active in mice.

BIOTIN

Biotin (Coenzyme R, Vitamin H, Anti-egg White Injury Factor or S or Skin Factor). In 1901, Wilders⁹⁷ observed that wort or similar extracts, in addition to fermentable sugars and inorganic salts, were necessary for growth and fermentation of yeast. It was thought that a heat stable organic substance was the active factor and it was provisionally called bios. Subsequently, it has been shown that a number of substances such as vitamin B₁, nicotinic acid, riboflavin, pyridoxine and β -alanine are growth factors for yeast. It was also shown that wild yeasts do not need bios and that it is needed only by highly cultivated yeasts.

One of the factors of bios could be adsorbed on charcoal and eluted with acetone ammonia. The name biotin was suggested for this substance. Kogel *et al.*⁹⁸ spent 5 years in order to isolate 70 milligrams of the methyl ester of biotin. Two parts per 100,000,000 of crystalline biotin stimulated the growth of yeast. Because of its marked

activity, it can be detected in a few milligrams of natural substances. About this time, Allison *et al.*⁹⁹ reported the presence of a substance called "coenzyme R" that was necessary for the growth of *Rhizobium*, a nitrogen fixing bacterium. Still others were working on a factor which would inhibit the marked deleterious effects produced by the feeding of raw egg white. This protective factor was called "factor X,"¹⁰⁰ "anti-egg white injury factor,"¹⁰¹ "vitamin H"¹⁰² or "skin factor." It subsequently was shown¹⁰³ that these activities were due to one substance, which is now called biotin. The terms "factor w," "vitamin B_w" and "bios 11_b," recorded in the literature in connection with nutritional studies, no doubt are also synonymous with biotin.

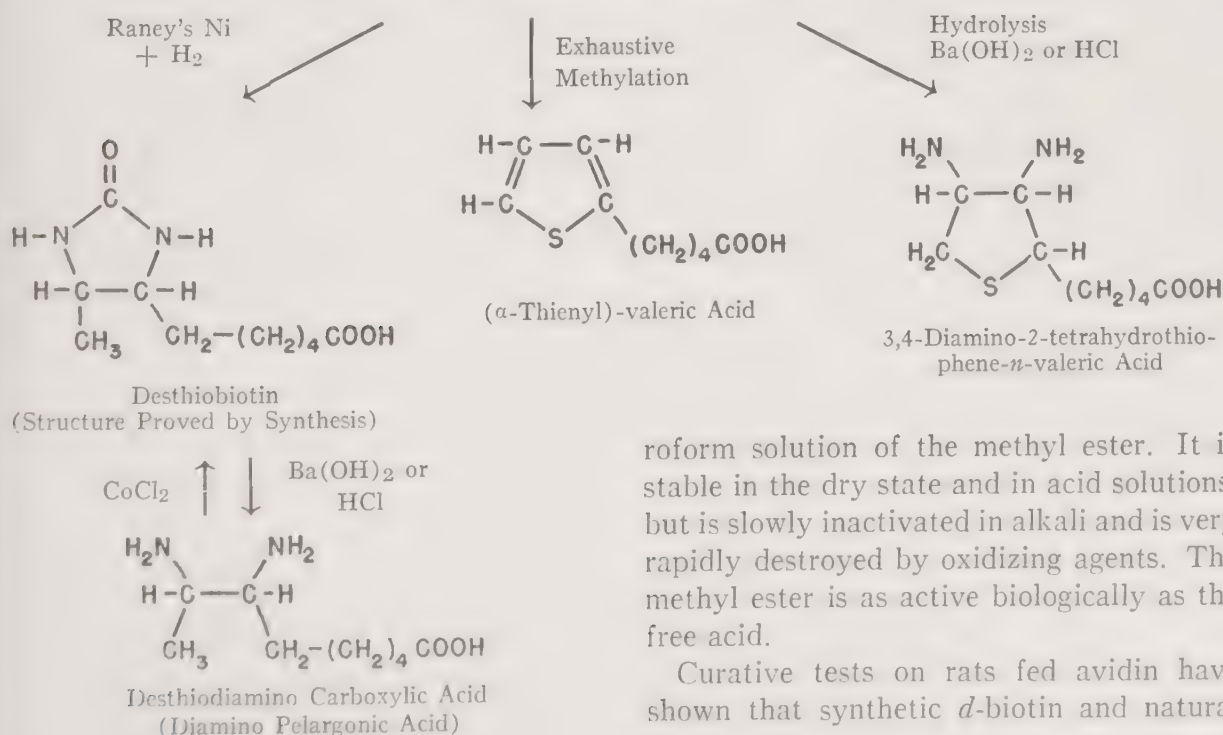
V. du Vigneaud *et al.* of Cornell University isolated sufficient quantities of biotin, in about 1941, from liver and milk by adsorption on aluminum oxide and elution with acetone and methanol, to be used in degradation studies together with Folkers *et al.* of Merck and Co. The following degradation in part served as clues to its composition and aided in its subsequent synthesis.

The synthesis of biotin (see page 516) was complicated by the number of isomers encountered. Trans fusion of the bicyclic system was ruled out on the basis of the strain involved. On this basis, four (instead of eight) isomers existing in two racemic modifications are indicated, and presumably biotin, which is optically active and optically stable, is one of the four.

Biotin occurs both free and combined even if in minute quantities in some cases. Small amounts are present in all higher animals. The highest concentrations are found in liver, kidney, eggs and yeast as a water-insoluble, firmly-bound complex. Considerable quantities are found both free and combined in vegetables, grains, nuts, etc. Alfalfa, string beans, spinach and grass are fair sources, while beets, cabbage, peas and potatoes are low in biotin. Peaches and raspberries are high in free biotin. The bound form seems to be as well utilized as the free form.

Biotin occurs as a white crystalline powder that melts at 230-232° C. It is optically active $[\alpha]_D = +92$ for a 0.3 per cent solution in 0.1 N sodium hydroxide or +57 for chlo-

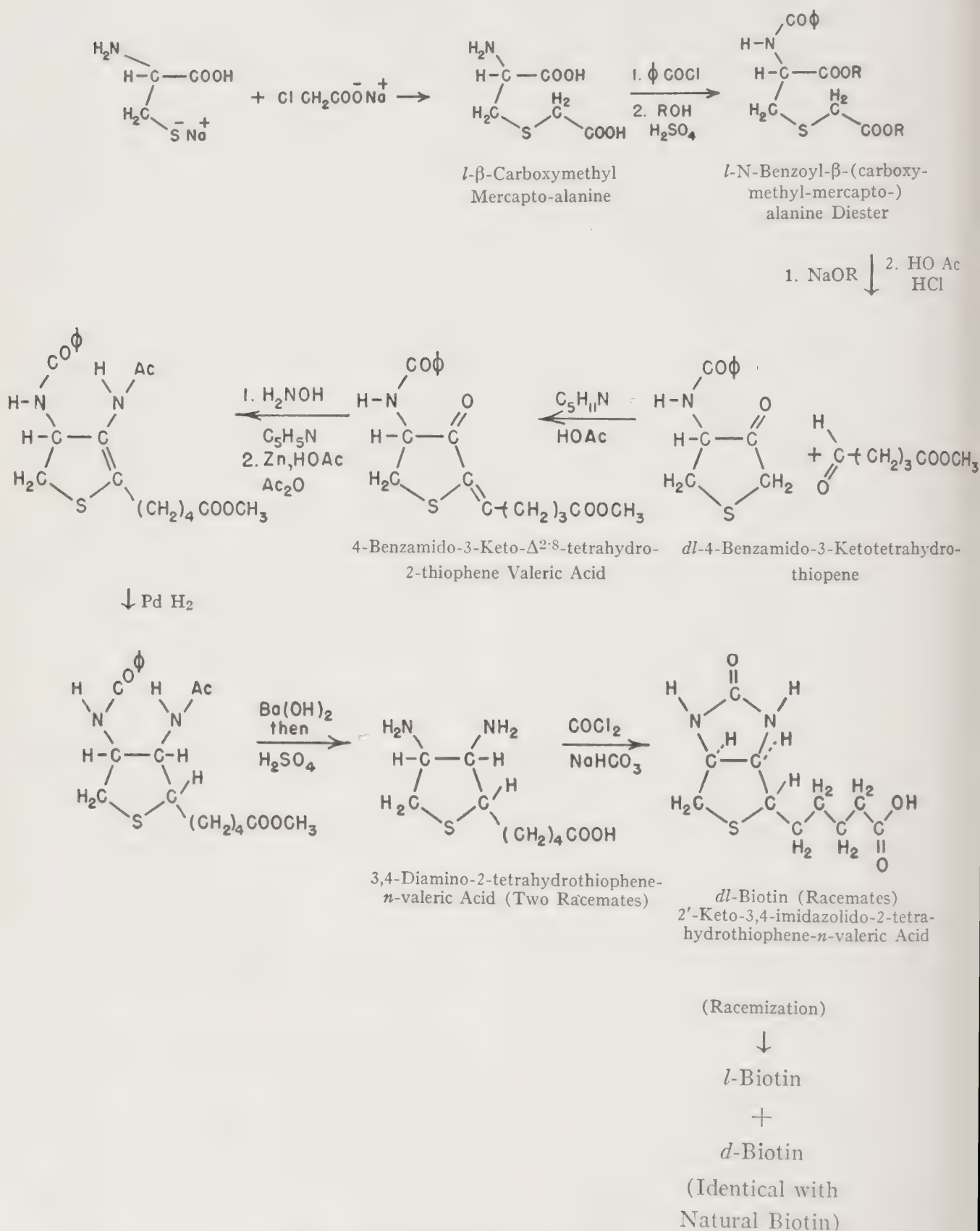
Degradation of Biotin¹⁰⁴



roform solution of the methyl ester. It is stable in the dry state and in acid solutions, but is slowly inactivated in alkali and is very rapidly destroyed by oxidizing agents. The methyl ester is as active biologically as the free acid.

Curative tests on rats fed avidin have shown that synthetic *d*-biotin and natural

Synthesis of Biotin



biotin are equal in activity. *dl*-Biotin is only half as active as *d*-biotin. *l*-Biotin is inactive when fed in seven and one half times the amount of *d*-biotin, and *dl*-allobiotin¹⁰⁵ was inactive in amounts ten times that of *d*-biotin.¹⁰⁶ *dl*-Oxybiotin has been synthesized¹⁰⁷ and its microbiologic activity for certain organisms has been shown to be equal to that of *dl*-biotin.^{107,108} It is also less active in animals. It seems likely that oxybiotin and biotin have identical spatial configurations and that the two compounds differ from one another only in the nature of the one hetero atom. *dl*-Oxybiotin is not converted by micro-organisms into *dl*-biotin. Although *dl*-7,8-diaminopelargonic acid, a degradation product of biotin, is inactive in rats, it and many other simpler molecules related or not related in structure to biotin are effective in some degree for yeast, *Lactobacillus casei*, diphtheria bacillus, etc. For example, pimelic acid, an expected degradation product of biotin, had a growth promoting property for diphtheria bacillus that was not inhibited by avidin.¹⁰⁹ 7,8-Diaminopelargonic acid is one-twentieth as active as biotin for yeast, which can convert it to biotin and utilize it even in the presence of avidin. Desthiobiotin is as active for yeast as is biotin, whereas, it inhibits the growth of *Lactobacillus casei*. Imidazolidone caproic and valeric acids are antibiotin factors for yeast, *Lactobacillus casei*, *Escherichia coli* and pneumococci I and II.

Biotin sulfoxide and biotin sulfone are active for yeast and are inhibited by avidin. They are inactive for *Lactobacillus casei*, and the latter has antibiotin activity for *Staphylococcus aureus*, for some streptococci and for pneumococci II, III and VIII, but not for *Escherichia coli*.

Evidence¹¹⁰ is presented that biotin may be a coenzyme in the enzymatic decarboxylation of oxalacetic acid.

Biotin deficiency in mammals develops only* when raw egg white is added to the biotin deficient diet. The first symptoms of

biotin deficiency in rats is a characteristic dermatitis around the eyes called "spectacle eye," which progresses to general alopecia and a scaly dermatitis. Raw egg white contains a substance called avidin which binds biotin in a nonabsorbable form. The avidin-biotin complex is excreted in the feces. Biotin causes the development in rats of fatty livers that are characterized by a high cholesterol content. The fatty liver effect of biotin can be prevented by the simultaneous feeding of lipocaic (an internal secretion of the pancreas) or inositol.

When large amounts of raw egg white (induced biotin deficiency) were fed to humans, the following symptoms were observed: a maculosquamous dermatitis of the neck, hands, arms and legs; striking ashy pallor of the skin and mucous membranes; a diminution in hemoglobin and erythrocytes; a rise in serum cholesterol; an atrophy of the papillae on the tongue; muscle pains; hyperaesthesia; lassitude and depression.

Certain cases of baldness in men are caused by seborrheic conditions and can be improved by biotin. Encouraging results were obtained in severe cases of seborrhea that seemed to be related to the skin disease called psoriasis.

ANTIHEMORRHAGIC VITAMINS

In 1929 Dam,¹¹¹ using a special fat-free diet, reported experimentally induced, in chicks, bleeding tendencies, accompanied by a tendency toward delayed blood clotting. Later he,¹¹² and others¹¹³ furnished strong evidence for the existence of a vitaminlike organic factor present in fresh cabbage or an ether extract of alfalfa, or putrefied fish meal, cereals, hog livers, etc. that would cure an experimentally induced condition in chicks.† This condition is characterized by

† Vitamin K deficiency can be induced in chickens, ducklings and goslings when maintained on a vitamin K free diet because, even though the intestinal bacteria can synthesize antihemorrhagic agents, absorption from the lower portion of the intestine is at a minimal in birds. This is not true of mammals, except in cases of faulty absorption.

* Because intestinal bacteria can synthesize biotin as well as some other factors of the B complex.

subcutaneous, intramuscular and abdominal hemorrhages. Dam¹¹² proposed the name vitamin K (Koagulations vitamin) for this new factor found in the unsaponifiable portion of certain fats.

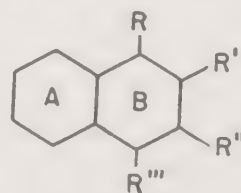
Vitamin K₁ was obtained in a crystalline form in 1937 from the unsaponifiable portion of alfalfa fat.¹¹⁴ Its yellow color, together with oxidation-reduction potential measurements, reductive acetylation and a broad absorption band with strong absorption in the region 240 to 275 mμ with a rather fine structure revealing sharp maxima at 243, 249, 260 and 270 mμ, indicated that vitamin K₁ contained a quinone structure of the 1,4 type. It was known that phthiacol and several natural pigments such as lapachol, etc., whose structures were known, exhibited some antihemorrhagic activity. These data, together with the following degradative studies, led to the proposal of a structure for vitamin K₁ that was verified by its synthesis in several laboratories.¹¹⁵ (For the degradation and synthesis of Vitamin K₁ see the equations on page 519.)

Alfalfa, chestnut leaves and spinach are excellent sources of vitamin K. It also occurs in hog-liver fat, hempseed, tomatoes, kale, soybean oil, etc. In most plants it appears to be confined to the green leafy parts. The highest concentrations of antihemorrhagic agents is present in certain micro-organisms which may be 11 to 38 times as active as alfalfa. These micro-organisms are *Bacillus cereus*, *B. mycoides*, *B. subtilis*, *Bacterium proteus*, *Mycobacterium tuberculosis*, *Sarcina lutea* and *Staphylococcus aureus*. Other micro-organisms produce little if any antihemorrhagic agents. Putrefied fish meal was used to prepare antihemorrhagic agents for clinical trial. This factor was shown to be vitamin K₂ or 2-methyl-3-difarnesyl-1,4-naphthoquinone.¹¹⁷ Crystalline vitamin K₂ melts at 50.5° C. and has chemical and physical properties similar to those of vitamin K₁. Whether this compound or vitamin K₁ occurs in the above mentioned organisms is not known.

Pure vitamin K₁¹¹⁸ is a yellow, crystalline solid that melts at 69° C. It is insoluble in water, soluble in methyl and ethyl alcohols and in the usual fat solvents. It is unstable toward light, oxidation, strong acids and halogens. It easily can be reduced to the corresponding hydroquinone, which in turn can be esterified. Vitamin K₁ gives the following color reaction.¹¹⁹ To a few milligrams of material in one or two cc. of methanol, one cc. of sodium methylate (2-3 grams of sodium in 50 cc. methanol) is added. If interfering pigments are practically absent, the mixture slowly develops a distinct purple color, providing sufficient vitamin K₁ is present. The color soon changes to a reddish-purple and finally to a reddish-brown. Certain synthetic α-naphthoquinones that have at least one allyl group in the quinoid ring give intense and transient blue or purple colors.

A large number of compounds have been tested for their antihemorrhagic activity, and the compounds in Table 54 (page 520) have been chosen because of their pronounced activity.

Significant biologic activity is manifested in the following compound when :



1. Ring A is aromatic or hydro-aromatic.
2. Ring A is not substituted.
3. Ring B is aromatic or hydro-aromatic.
4. R equals OH; CO; OR; OAc; (the R in OR equals methyl or ethyl).
5. R' equals methyl.
6. R'' equals H, sulfonic acid, dimethyl-amino or an alkyl group containing 10 or more than 10 carbon atoms. A double bond in the β, γ-position of this alkyl group enhances potency, whereas, if the double bond is further removed, it exerts no effect. Isoprenoid groups are more effective than straight chains.

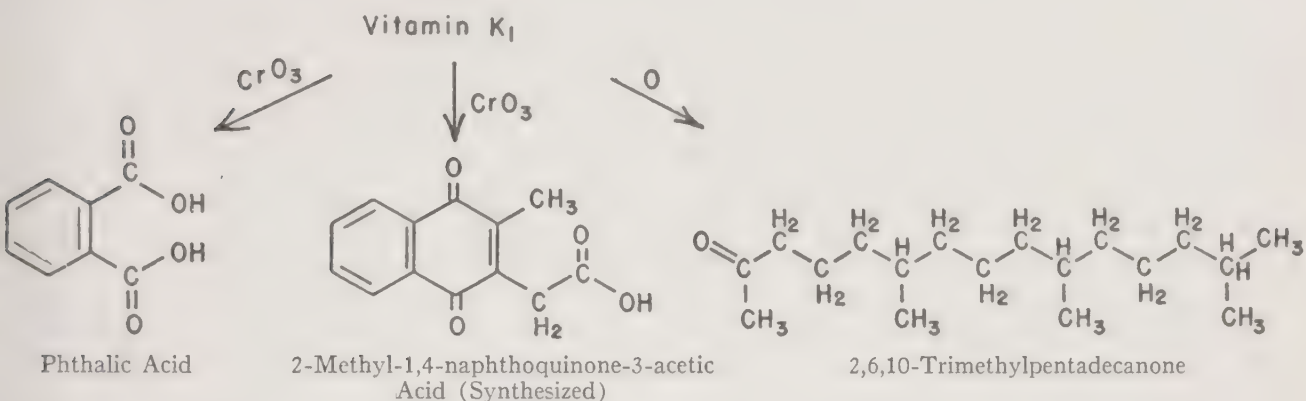
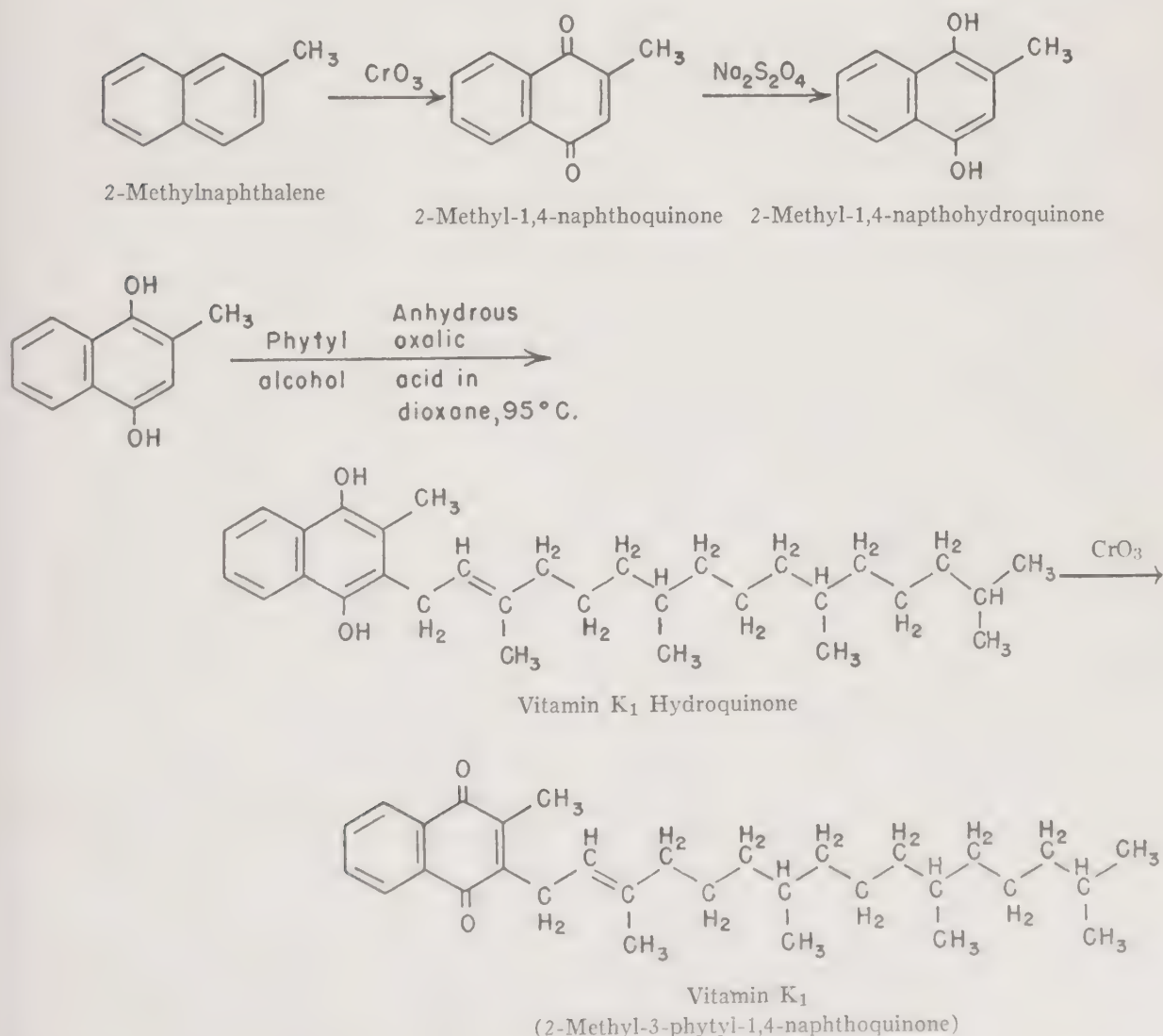
Degradation of Vitamin K₁

Synthesis of Vitamin K₁


TABLE 54. ANTIHEMORRHAGIC AGENTS AND THEIR EFFECTIVE DOSES

ANTIHEMORRHAGIC AGENT	EFFECTIVE DOSE IN MICROGRAMS*
2-METHYL-3-ALKYL AND 3- β -ALKENYL-1,4-NAPHTHOQUINONES	
2-Methyl-3-phytyl-1,4-naphthoquinone	1.0
2- " -3-farnesyl-1,4-naphthoquinone	5.0
2- " -3- β - γ -dihydrophytyl-1,4-naphthoquinone	8.0
2- " -3-geranyl-1,4-naphthoquinone	25.0
2- " -3-cinnamyl-1,4-naphthoquinone	25.0
2-ALKYL- AND 2- β -ALKENYL-1,4-NAPHTHOQUINONES	
2-Methyl-1,4-naphthoquinone	0.3
2-Phytyl-1,4-naphthoquinone	50.0
NAPHTHOQUINONE OXIDES	
Vitamin K ₁ oxide	1.2
2-Methyl-1,4-naphthoquinone oxide	5.0
2,3-Dimethyl-1,4-naphthoquinone oxide	25.0
WATER-SOLUBLE INORGANIC ESTERS	
Sodium 2-methyl-1,4-naphthohydroquinone diphosphate	0.5
Sodium 2-methyl-1,4-naphthohydroquinone disulfate	2.0
Vitamin K ₁ hydroquinone diphosphoric acid	50.0
ESTERS AND ETHERS	
2-Methyl-1,4-naphthohydroquinone dibenzoate and diacetate	1.0
Dimethyl ether	5.0
Monomethyl ether	1.0
Dibenzyl ether	7.0
REDUCTION PRODUCTS OF VITAMIN K ₁ AND 2-METHYLNAPHTHOQUINONE	
5,8-Dihydrovitamin K ₁	4.0
2-Methyl-5,8-dihydro-1,4-naphthoquinone	6.0
2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone	8.0
METHYLNAPHTHOLS, METHYLTETRALONES AND RELATED COMPOUNDS	
2-Methyl-1-naphthol	1.0
3- " -1-naphthol	0.6
3- " -1-tetralone	1.0
2- " -1-tetralone	0.6
2- " -1-naphthylamine	5.0
NAPHTHOHYDROQUINONES	
2-Methyl-1,4-naphthohydroquinone	0.5

* The minimum amount of each compound given orally in one dose (dissolved in 0.1 cc. peanut oil) that will reduce the clotting times of 60 to 80 per cent of vitamin K deficient chicks to less than 10 minutes in a period of 18 hours.¹²⁰

7. R''' equals H, OH, NH₂, CO, OR, OAc,
 (the R in OR equals methyl or ethyl).
 Decreased antihemorrhagic activity is
 obtained when:

1. Ring A is substituted.
2. R' is an alkyl group larger than a methyl group.
3. R'' is a hydroxyl group.

4. R'' contains a hydroxyl group in a side chain.

It is interesting to note that, if ring A is benzenoid in character, the introduction of sulfur in place of a $-\text{CH}=\text{CH}-$ in this ring in 2-methylnaphthoquinone, permits the retention of some antihemorrhagic activity.¹²¹ This might indicate that, in the process of exerting vitamin K activity, the benzenoid end of the molecule must fit into a pocket carefully tailored to it. That the other end is not so closely surrounded is shown by the retention of activity on changing the alkyl group in the 2-position.

Although marked antihemorrhagic activity is found in a large number of compounds, the possibility exists that they may be converted in the body to a vitamin K₁ type compound. The esters of the hydroquinones may be hydrolyzed, and the resulting hydroquinone may be oxidized to the quinone. The methyl tetralones, which are very active, could possibly be dehydrogenated to the methylnaphthols, which are hydroxylated, and the latter product converted to the biologically equivalent quinone. Compounds with a dihydrobenzenoid ring (such as 5,8-dihydrovitamin K₁) appear to be moderately dehydrogenated, whereas the corresponding tetrahydrides are resistant to such a change.

Antihemorrhagic agents, such as vitamin K₁, are one of the limiting factors in the production of normal amounts of prothrombin by the liver. The presence of adequate amounts of prothrombin in the blood is one of the limiting factors in normal blood clotting. It is highly probable that the vitamin K is a prosthetic group (coenzyme) whose function is not definitely known. The view that vitamin K is a prosthetic group is substantiated somewhat by the fact that a number of compounds, such as the sulfonamides, salicylic acid, Dicoumarol, etc., are hemorrhagic agents and prevent the production of prothrombin. This, because they possibly compete for the position of the pros-

thetic group (vitamin K) in the prothrombin molecule to produce a nonfunctioning form of prothrombin.

It follows that any condition which does not permit the full utilization of the antihemorrhagic agents or the production of prothrombin would lead to an increased amount of time in which the blood would clot or to hemorrhagic conditions. Some of these conditions are: (1) faulty absorption caused by a number of conditions, i.e., obstructive jaundice, biliary fistulas, intestinal polyposis, chronic ulcerative colitis, intestinal fistula, intestinal obstruction and sprue; (2) damaged livers or primary hepatic diseases, such as atrophy, cirrhosis or chronic hepatitis; (3) insufficient amounts of bile or abnormal bile in the intestinal tract and (4) insufficient amounts of vitamin K.

Bile of a normal composition is necessary to facilitate the absorption of vitamin K from the intestinal tract. The bile component principally concerned in the absorption and transport of fat-soluble vitamin K from the digestive tract is thought to be deoxycholic acid. The molecular compound of vitamin K with deoxycholic acid was effective upon oral administration to bile-fistula rats. A crude vitamin K-deoxycholic acid preparation in aqueous solution was found effective by subcutaneous injection into deficient chicks, whereas an emulsion of the crude vitamin was effective by intramuscular, but not by subcutaneous, injection.

Vitamin K is administered in conjunction with bile salts or their derivatives in pre- and postoperative jaundiced patients to bring and maintain a normal prothrombin level in the blood.

In the average infant, the birth values of prothrombin content are adequate, but during the first few days of life they appear to fall rapidly, even dangerously low, and then slowly recover spontaneously. This transition period was and is a critical one because of the numerous sites of hemorrhagic manifestations, traumatic or spontaneous, that

may prove serious if not fatal. This condition is now recognized as a type of alimentary vitamin K deficiency. The spontaneous recovery is due perhaps to the establishment of an intestinal flora capable of synthesizing vitamin K after ingestion of food. However, administration of vitamin K orally effects a prompt recovery.

Vitamin K can be used to diagnose accurately liver function. The intramuscular injection of 2 milligrams of 2-methyl-1,4-naphthoquinone has led to response in prothrombin index in patients with jaundice of extrahepatic origin, but not in patients with jaundice of intrahepatic origin, e.g., cirrhosis.

Vitamin K₁ N.N.R. occurs as a yellow, very viscous, nearly odorless liquid that is insoluble in water; it is soluble in the common organic solvents and vegetable oils. It may be isolated from natural sources or prepared synthetically.

The average dose is 4 to 10 mg. for adults, either by mouth or intravenously.

Menadione (2-Methyl-naphthoquinone, Menaphthene, Menaphthone), U.S.P. (2-Methyl-1,4-naphthoquinone, Thyloquinone). Menadione can be prepared very readily by the oxidation of 2-methyl-naphthalene with chromic acid. It is a bright yellow, crystalline powder, and is nearly odorless. It is affected by sunlight. Menadione is practically insoluble in water; it is soluble in vegetable oils and one gram of it is soluble in about 60 cc. of alcohol. The U.S.P. has a caution that menadione powder is irritating to the respiratory tract and to the skin, and an alcoholic solution has vesicant properties.

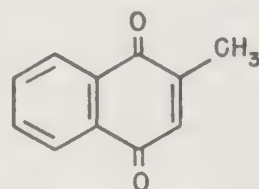
On a mole for mole basis, menadione is equal to vitamin K₁ in activity and can be used as a complete substitute for this vitamin. It is effective orally, intravenously and intramuscularly. If given orally to patients with biliary obstruction, bile salts or their equivalent should be administered simultaneously in order to facilitate absorption. It can be administered intramuscularly in oil

when the patient cannot tolerate an oral product, has a biliary obstruction or where a prolonged effect is desired. Although the U.S.P. states that menadione is insoluble in water, it is sufficiently soluble in water (0.1 to 0.13 milligrams per cc.) to allow its use intravenously.

It has been shown that 2-methyl-1,4-naphthoquinone inhibits the glucose metabolism of the parasite causing schistosomiasis and, in conjunction with subcurative doses of fuadin, eliminates parasites from the intestinal blood vessels of mice.

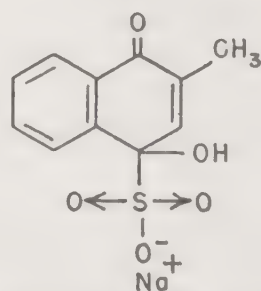
The average dose is 1 mg.

Menadione Sodium Bisulfite (Menadione Bisulfite) U.S.P. is prepared by adding a solution of sodium bisulfite to menadione.



Menadione

↓ NaHSO₃



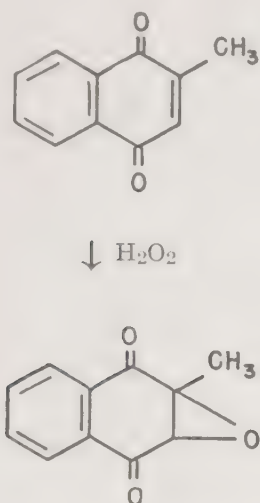
Menadione Sodium Bisulfite

Menadione sodium bisulfite occurs as a white, crystalline, odorless powder. One gram of it dissolves in about 2 cc. of water, and it is slightly soluble in alcohol. It decomposes in the presence of alkali to liberate the free quinone.

This is a water-soluble form of menadione, and the U.S.P. average dose for intramuscular or intravenous use is 2 milligrams.

Oxides. The oxides¹²² of menadione, vitamin K, etc., can be prepared by the action of hydrogen peroxides, in alkaline solution,

upon the parent compound. For example, 2-methyl-1,4-naphthoquinone oxide can be prepared as follows:

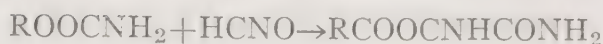
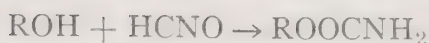


This type of compound appears to counteract the hemorrhagic effect of Dicoumarol more effectively than menadione or vitamin K_1 .

THE VITAMINS E

In 1922, Evans and Bishop¹²³ showed that rats maintained on certain diets did not produce offspring, although normal growth occurred and the rats seemed normal in other respects. They, therefore, postulated that some factor, unrelated to the known dietary essentials, controlled fertility and temporarily called this factor X. Later Sure¹²⁴ noted the same phenomenon and proposed the name "vitamin E" for the factor essential for reproduction. This condition was corrected by the addition of lettuce, whole wheat, dry cereals, corn, etc. to the diet. It was soon shown that the unsaponifiable portions of certain natural oils would exert the same effect.

Much difficulty was encountered in preparing a pure fraction from the unsaponifiable portions of oils. Evans *et al.*,¹²⁵ however, succeeded in isolating from wheat germ oil an active substance in the form of a crystalline monoalphanate, which melted at 158-160° C. The regenerated alcohol was

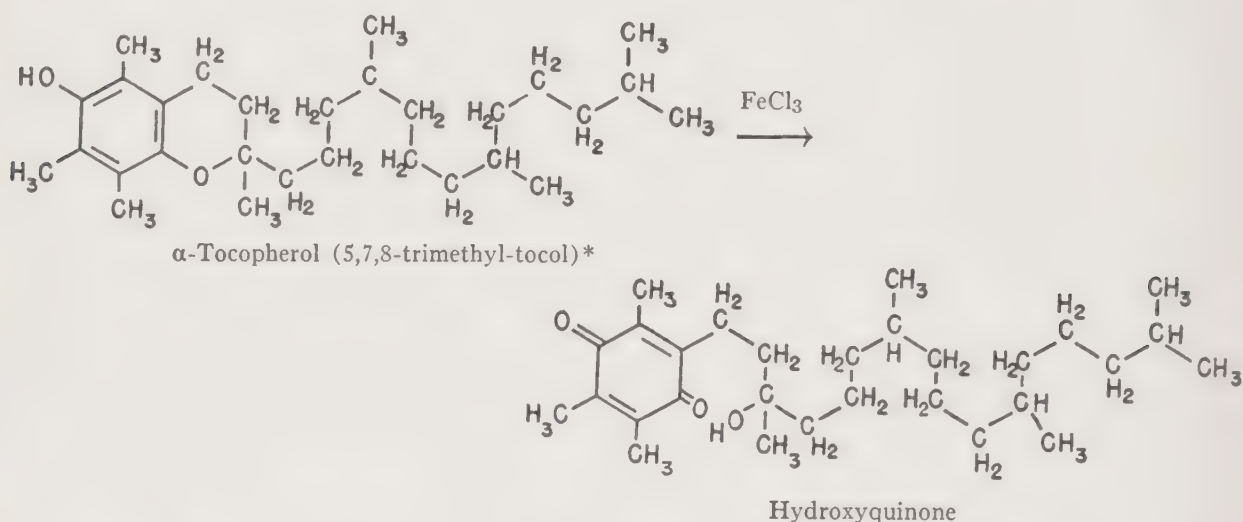
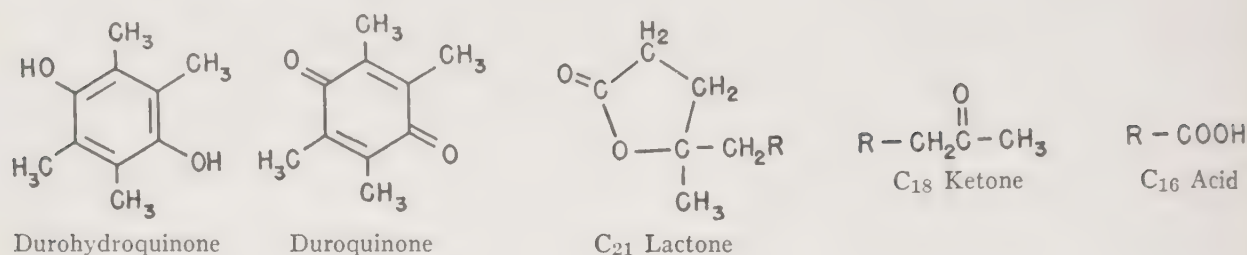


an oil and agreed with the formula $\text{C}_{29}\text{H}_{50}\text{O}_2$. In single doses of one to three milligrams, it will produce litters in 50 per cent of the pregnant rats that have been maintained on a diet deficient in this or similar factors. This factor was given the name α -tocopherol, from *Tokos* meaning "child" and *pherein* "to bear" and the ending *-ol* indicating an alcohol. A second alphanate which melted at 144.6° C. was obtained. The regenerated substance was also an oil and agreed with the formula $\text{C}_{28}\text{H}_{48}\text{O}_2$. It was called β -tocopherol and was originally reported to be biologically active in single doses of 8 milligrams. In addition to α - and β -tocopherols, γ -tocopherol was isolated as the alphanate, m.p. 138-140° C., from cottonseed oil.¹²⁶ Although the activity of this compound was originally reported to be equal to that of β -tocopherol, reinvestigations have shown it to be only one one-hundredth as active as α -tocopherol.¹²⁷ A fourth tocopherol, i.e., δ -tocopherol,¹²⁸ has been isolated from soy bean oil, in which it comprises 30 per cent of the tocopherols of this oil. Its biologic activity is equal to that of γ -tocopherol.

The degradation of α -tocopherol by thermal decomposition* at 350° C. yielded durohydroquinone and a red oil, and heating with selenium yielded duroquinone and a red oil. Oxidation with chromic acid gave diacetyl, acetone, dimethyl maleic anhydride, a C_{21} lactone, a C_{18} methyl alkyl ketone and a C_{16} acid. The R group in the following fragments was shown to contain enough methyl groups to indicate that they might be composed of reduced isoprene units joined head to tail. Further careful oxidation of α -tocopherol yielded a yellow quinone containing a tertiary alcohol group. A compound with such a structure could only come from a chroman type compound in which the ring

* Many alkyl ethers of phenols are cleaved by pyrolysis to the phenol and an unsaturated hydrocarbon.

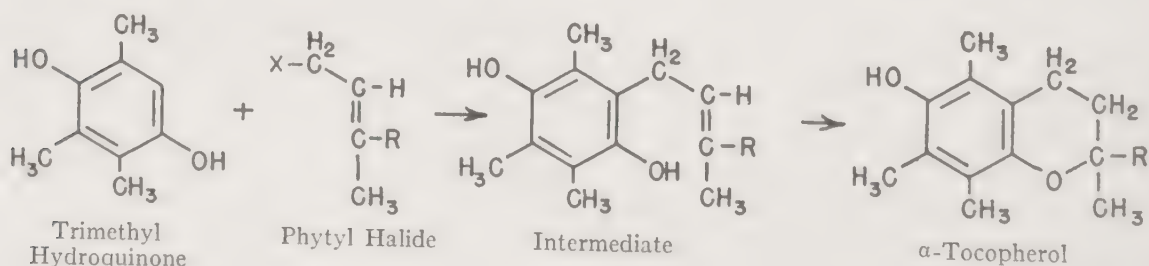
involved and the side chain are composed of reduced isoprene units.



Karrer¹³⁰ postulated that the tocopherols could be conceived as end-products of the condensation of di- and trimethylhydroquinones and phytol. Fernholz¹³¹ was the first to suggest that the correct formula for α -tocopherol should contain a chroman ring. α -Tocopherol was synthesized¹³² in a number of different laboratories by condensing durohydroquinone and phytol, phytol bromide or phytadiene. When the halide is used, no solvent or catalyst is needed; however, when the alcohol or diene is used, it is more advantageous to use a catalyst and a solvent. One of these syntheses can be depicted as follows:

Ring closure of the above intermediate involves the addition of the hydroxyl group to the double bond in the side chain in accordance with Markownikoff's rule. The nature of the ring structure, i.e., coumaran or chroman in the final product, is determined by the type of substitution at the carbon atom in the allylic compound. Dialkyl substitution at the carbon atom gives rise to the chroman ring, whereas if hydrogens are present, the product will be a coumaran.

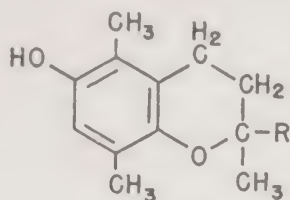
Degradative and synthetic studies comparable to those used in connection with α -



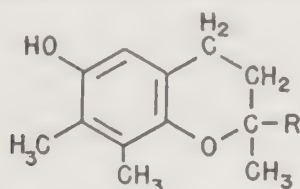
* Nomenclature proposed by P. Karrer and H. Fritzsche.¹²⁹

tocopherol have been applied to β , γ and δ -tocopherols, and they have been shown to

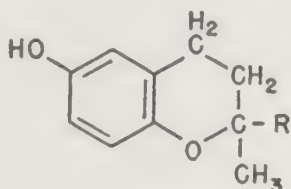
have the following structures.



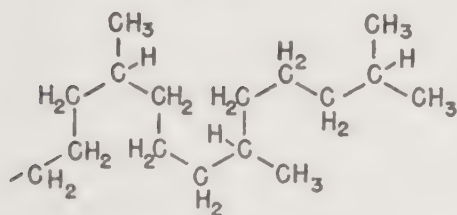
β -Tocopherol
(*p*-Xylotocopherol or 5,8-Dimethyl Tocol)



γ -Tocopherol
(*o*-Xylotocopherol or 7,8-Dimethyl Tocol)



δ -Tocopherol
(Tocol)



R equals the above radical

The syntheses of β - and γ -tocopherols proved to be much more difficult than the synthesis of α -tocopherol, by virtue of the fact that the reactants gave rise to complicated mixtures which were very difficult to resolve.

The tocopherols are light-yellow, viscous, odorless oils that have an insipid taste. They are insoluble in water, but are soluble in alcohol, organic solvents and fixed oils. They are stable in air for reasonable periods of time, but are slowly oxidized by air. They are oxidized readily by ferric salts, mild oxidizing agents, and by air in the presence of alkali. They rapidly are inactivated by exposure to ultraviolet light; however, not all samples behave alike in this respect because traces of impurities apparently affect the rate of oxidation very much. The tocopherols

have antioxidant properties for fixed oils in the following decreasing order of effectiveness: δ -, γ -, β - and α -.¹³³ In the process of acting as antioxidants, the tocopherols are destroyed by the accumulating fat peroxides that are decomposed by them. The tocopherols can be converted to the acetates and benzoates, respectively, which are oils and are as active as the parent compounds but have the advantage of being more stable toward oxidation.

The tocopherols are especially abundant in wheat germ, rice germ, corn germ, other seed germs, lettuce, soya and cottonseed oils. All green plants contain some tocopherols, and there is some evidence that some green leafy vegetables and rose hips contain more than wheat germ. It is probably synthesized by leaves and translocated to the seeds. All four tocopherols have been found in wheat germ oil. α -, β - and γ -tocopherols have been found in cottonseed oil. Corn oil contains predominantly γ -tocopherol and thus furnishes a convenient source for the isolation of this, a difficult member of the tocopherols to prepare. δ -Tocopherol is 30 per cent of the mixed tocopherols of soya bean oil.

Synthetic *dl*- α -tocopherol is equal to the naturally occurring α -tocopherol in activity. β -Tocopherol is about one-half as active as α -tocopherol, and the γ - and δ -tocopherols are only one-hundredth as active as α -tocopherol. Meta-xylo-tocopherol, prepared synthetically, is active at the 3 milligram level, which is about equal to α -tocopherol. The esters of the tocopherols, such as the acetate, propionate and butyrate, are more active than the parent compound.¹³⁴ This is also true of the phosphoric acid ester of *dl*- δ -tocopherol when it is administered parenterally.¹³⁵ The ethers of the tocopherols are inactive. The oxidation of the tocopherols to their corresponding quinones also leads to inactive compounds. Replacement of the methyl groups by ethyl groups leads to decreased activity. The introduction of a double bond in the 3,4- position of α -tocopherol reduces its activity by about two-thirds. Reduction of the size of the long alkyl side chain or the introduction of double

bonds in this side chain markedly reduced activity. Many synthetic compounds¹³⁶ have been tested for their activity, and forty of these are distributed among a half a dozen chemical classes and show some activity, though of a low order. Some of the simpler compounds that show activity are *o*- and *p*-xylo-hydroquinone, trimethylhydroquinone, durohydroquinone, the esters of these hydroquinones, *o*-allyl-phenol, *p*-amino-*o*-allyl-phenol, 2,3-dimethyl-5,6,7,8-tetrahydro-1,4-naphthoquinone, chroman, 2,2-diethyl chroman, 5,7,8-trimethyl-2-carboethoxy coumarin, 2-methyl-coumaran and 2,2,7-trimethyl coumaran.

It is interesting to note that naphtho-tocopherol, which is active at the 25 milligram level, also exhibits vitamin K activity in doses of 300 to 600 micrograms.

The exact role that the tocopherols play in the animal body is not known. They apparently play an essential part in the metabolism of skeletal muscle in all species of mammals that have been investigated and in ducklings. Tocopherols are concerned with contractile rather than with the resting metabolism of muscle.¹³⁷

It is interesting and perhaps significant that the administration of 100 milligrams of α -tocopherol quinone to pregnant mice brought about resorption of the fetus and hemorrhage, but a like amount was without effect in nonpregnant animals. This effect was not prevented by giving α -tocopherol acetate; however, vitamin K was the only compound tested that was effective in reversing the effect of α -tocopherol quinone.

Male rats maintained on a diet deficient in the tocopherols suffer a degeneration of the germinal epithelium of the testicular seminal tubules with the resultant complete liquefaction of the sperm nuclei. Although recovery can be effected in the early stages by the administration of the tocopherols, if advanced depletion is to be treated successfully, tocopherol therapy is required for about a year.

In the case of tocopherol-depleted females,

the normally fertilized eggs start their journey to the uterus, but within a few days the embryos, which have become anchored to the uterine wall, exhibit visible and morphologic changes and gradually die. The dead fetuses are resorbed; this has no effect upon the next estrus cycle and conception can occur again. If tocopherol-containing materials are fed to a depleted female a day or so after conception, the pregnancy will be terminated by the birth of a litter of living young. This procedure can be used to test various materials for their activities. This activity is often expressed as the milligrams of the substance, fed in a single dose, necessary to cure the sterility and to produce litters in 50 per cent of the animals used. The litter of a depleted female cannot be saved by the administration of tocopherols after the fifth day of gestation.

Nurslings reared on a tocopherol-deficient female rat develop paralytic symptoms that can be prevented by the administration of tocopherols directly to the nurslings. This observation led to the use of this vitamin in muscular dystrophies and related conditions in humans, for example, fibrositis, which is defined as an inflammatory reaction of fibrous connective tissue and may occur either as a primary or secondary disease. Many common diseases show evidence of primary fibrositis but masquerade under other terms, i.e., muscular rheumatism, lumbago, tenonitis periarticular fibrositis, torticollis, myositis and panniculitis. Some muscular disorders are being treated effectively by α -tocopherol.

Evidence to date would indicate that α -tocopherol or its equivalent may be of value in habitual abortion in some cases.¹³⁸

The International Standard is one milligram of synthetic racemic α -tocopherol acetate. The latter is available as the proprietary product Ephynal Acetate. This is the average amount which, when administered orally, prevents resorption-gestation in rats deprived of vitamin E. One rat unit is the smallest amount of vitamin E which,

when given per os daily to resorption-sterile female rats for the entire period of gestation (21 days), results in the birth of at least one living young in 50 per cent of the animals.

PANTOTHENIC ACID

Pantothenic Acid (Chick Antidermatitis Factor). In 1933, R. J. Williams *et al.*¹³⁹ reported that extracts of very diverse tissues representing many different biological groups, i.e., chordates, arthropods, echinoderms, molluscs, annelids, platyhelminthes, myxomycetes, bacteria, fungi, molds, algae and spermatophytes, all contain a substance that was capable of stimulating to a very marked degree the growth of Gebrude Mayer yeast. This property of growth stimulation was a convenient way with which to trace the concentration and isolation of the active substance. By this method the active substance can be detected quantitatively when only 5 parts per 10 billion are present. This was fortunate because liver, one of the richest sources of this factor, contains only 40 parts per million. The active concentrates from diversified sources, even though they contained some impurities, behaved so nearly uniformly that the same factor was thought to be present in all of them. The active substance appeared to be an acid and, since its occurrence was so wide spread, it was called "pantothenic acid," from the Greek meaning "from everywhere."

In 1938, Williams *et al.*^{140,141} reported the isolation of one-tenth of an ounce of crude pantothenic acid from 500 lbs. of raw liver, employing a very complicated process accompanied by 700 fractionations of an alkaloidal salt of the acid. He recognized that β -alanine was one cleavage product, and the other appeared to be dihydroxyvaleric acid. In the same year, Elvehjem *et al.*¹⁴² pointed out that the chick antidermatitis factor and pantothenic acid were similar in chemical properties. At the same time, Jukes¹⁴³ showed that the chick antidermatitis factor and calcium pantothenate supplied by Wil-

liams had the same biologic activity. In 1940, Williams and Major reported the synthesis of pantothenic acid as shown in the first set of equations at the top of page 528.¹⁴⁴

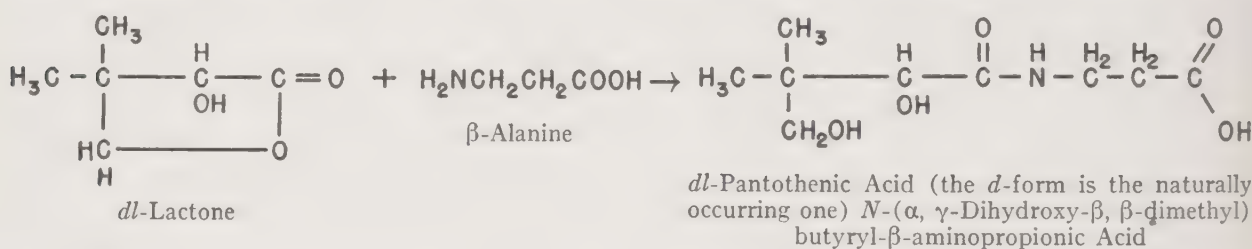
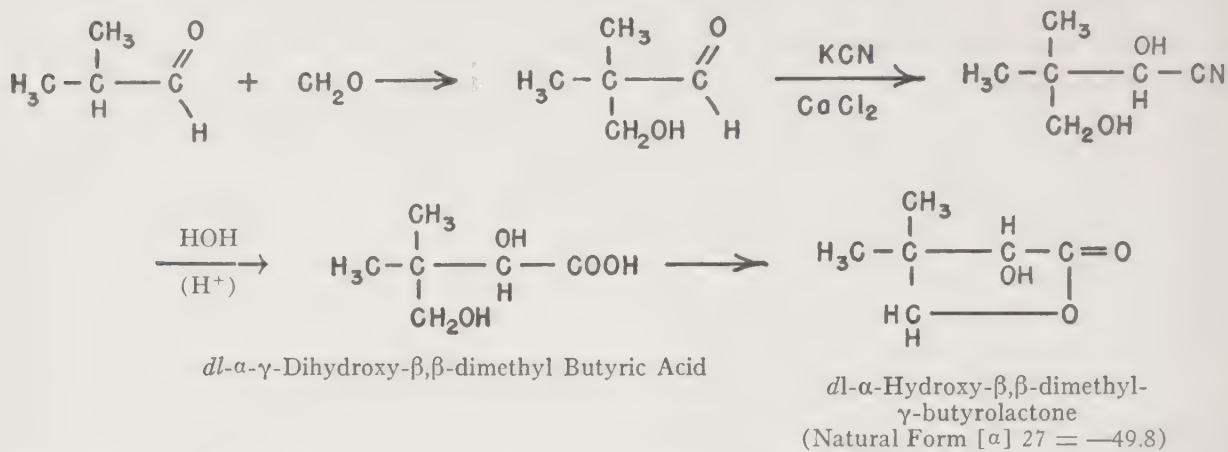
Both β -alanine and β -alanine ester are prepared in a number of ways and condensed in a number of ways with the acid chloride of the diacetate of the dihydroxy acid, the sodium salt of the dihydroxy-acid or the lactone to yield the desired pantothenic acid, which is a mixture of the *d*- and *l*-forms. (See the second set of equations on page 528.)

Pantothenic acid occurs as an odorless, white, microcrystalline powder. It is very soluble in water and is unstable in acid and alkaline solutions. Autoclaving calcium pantothenate at 120° C. for 20 minutes may cause a 10 to 30 per cent decomposition. A 5 per cent aqueous solution of calcium pantothenate has a pH of 7 to 8. In the solid state, both the free acid and the calcium salt are light-stable.

The richest sources¹⁴⁵ of pantothenic acid are liver, yeast, cereal brans, leafy vegetables, dairy products and eggs. It is produced by various molds and micro-organisms in the soil and elsewhere by green plants after they develop their capacity for photosynthesis. In some natural sources, such as liver, pantothenic acid occurs in a bound form from which it can be released by enzymatic activity.

Levorotatory pantothenic acid is biologically inactive. Ethyl pantothenate and ethyl monoacetylpantothenate are active in rats and chicks, but are not utilized by micro-organisms. In certain tests, fragments of the pantothenic acid molecule are active. For example, β -alanine stimulates the growth of yeast, certain strains of bacteria and is partially effective for the rat but ineffective in chicks.

A large number of compounds¹⁴⁶ have been prepared that are related in structure to pantothenic acid. With few exceptions, all compounds made had little or no activity. Replacement of the carboxyl group by an



alcohol, amine, nitrile, alkylamine, sulfone, sulfonamide, substituted sulfone or substituted sulfone amide groups yields inactive to partially active compounds. The loss of the α-hydroxyl group, the substitution of other amino acids for β-alanine or a change in the structure of the α-, γ-dihydroxy-β, β-dimethyl butyric acid portion of the molecule results in marked diminution to complete loss of activity. In fact, many of these compounds are antagonists of *d*-pantothenic acid activity, a property that varies in degree, depending on the organism used in the test. Some of the most effective pantothenic acid antagonists are *d*- and *l*-pantoyltaurine and *d*- and *l*-pantoyltaurine amide. *d*-Pantoyltaurine is about 32 times more active in this respect than the *l*-form for certain bacteria. This antagonistic effect is reversed by pantothenic acid; on the other hand, the antagonistic activity of 2-desoxypantothenic acid and the γ-hydroxy-*n*-butyl β-alanine is not reversed by pantothenic acid. α-Methylpantothenic acid is as active as pantothenic acid as a growth stimulant for certain bacteria.

Chicks maintained on a diet deficient in pantothenic acid develop a dermatitis that has been characterized as follows:¹⁴⁷ "External manifestations appear chiefly at the eyes, corners of the mouth and upon the legs and feet. The feathering is retarded and very ruffled because birds peck at themselves continuously. The crusty scabs at the corners of the mouth gradually enlarge and often involve the margins of the skin around the nostrils and underneath the lower mandible." Feather depigmentation occurs in black fowl.

Rats, dogs and hogs suffer severe pantothenic acid deficiency symptoms. Rats cease to grow after 3 to 4 weeks, show adrenal hemorrhages, scant, coarse fur with rusty spots, inflammation of the nose and blood-caked whiskers. Piebald and black rats also show a characteristic depigmentation of the fur, a condition which in most cases can be brought to normal by sufficiently large doses of pantothenic acid. In this induced achromotrichia, a highly individualistic response with regard to restoration of color was obtained upon pantothenic acid therapy, and

it is possible that other factors such as *p*-aminobenzoic acid, biotin and inositol may play some role. This is due to the fact that under the stimulus of vitamin B₁ or *p*-aminobenzoic acid, pantothenic acid, biotin and inositol are synthesized by the intestinal flora. Furthermore, in experiments where sulfa drugs were used to control the intestinal flora, experiments with various nutritional factors suggest that, for the proper utilization of pantothenic acid by the rat, "folic acid" in addition to biotin must be available.¹⁴⁸ It is probable that the effect of "folic acid" on pantothenic acid utilization occurs only in the presence of biotin since significant growth response in the rat (maintained on certain diets and sulfa drugs) follows the administration of folic acid only when biotin is also given.

Adult female rats failed to reproduce when they were deficient in pantothenic acid.

Pantothenic acid deficiency in the dog is characterized by hemorrhagic degeneration of the kidney, severe lesions in the stomach and intestines, mottled fatty livers and mottled thymuses.¹⁴⁹ They may eat normally up until a day or two of their death, which is accompanied by sudden prostration, coma or convulsions.

Pantothenic acid deficiency symptoms in hogs are similar to those in dogs.

The concentration of pantothenic acid in the blood of humans suffering from vitamin B complex deficiency is from 23 to 50 per cent lower than that found normally.

PYRIDOXINE

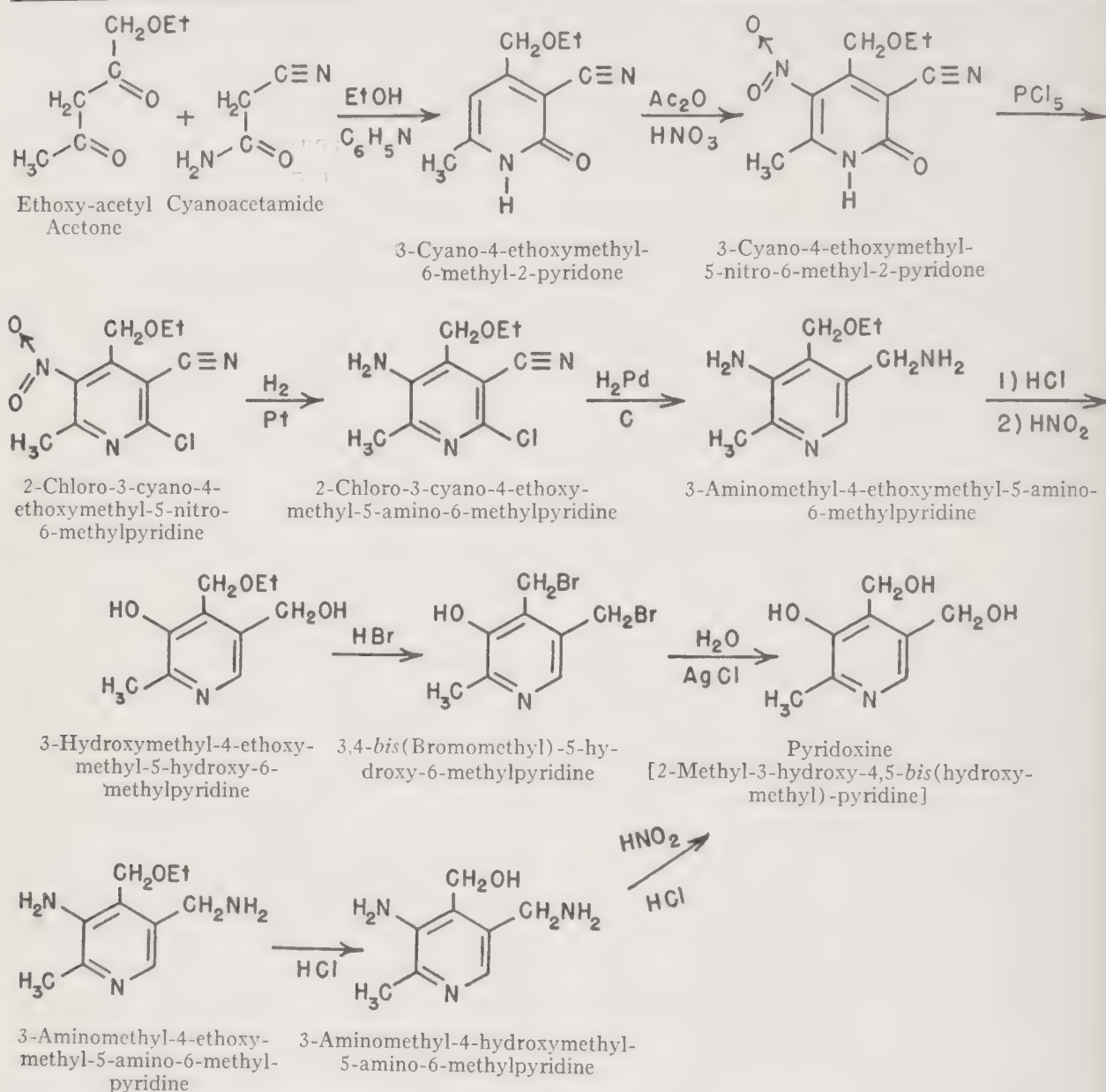
Pyridoxine (Vitamin B₆, Factor Y or Factor I, Rat Antidermatitis Factor). In 1935, P. Gyorgyi¹⁵⁰ showed that "rat pellagra" was not the same as human pellagra but that it resembled a particular disease of infancy known as "pink disease" or acrodynia. This "rat acrodynia" is characterized by a symmetrical dermatosis affecting first the paws and tips of the ears and nose. These areas become swollen, red and edema-

tous, with ulcers developing frequently around the snout and on the tongue. Thickening and scaling of the ears is noted and there is a loss of weight, with fatalities occurring in from one to three weeks after the appearance of the symptoms. Gyorgyi was able to cure the above conditions with a supplement obtained from yeast which he called "vitamin B₆." In 1938, this factor was isolated from rice paste and yeast in a crystalline form in a number of laboratories.¹⁵¹ A single dose of about 0.1 milligram produced healing in 14 days in a rat having severe vitamin B₆ deficiency symptoms.

Chemical tests, electrometric titration determinations and absorption spectrum studies gave clues as to its composition. These were substantiated by the synthesis of vitamin B₆ (1938 and 1939) as is shown in the equations at the top of page 530.¹⁵²

Pyridoxine hydrochloride is a white, odorless, crystalline substance that is readily soluble in water, sparingly soluble in alcohol and acetone and insoluble in ether. It is relatively stable to light and air in the solid form and in acid solutions at a pH of not greater than 5, at which pH it can be autoclaved at 15 lbs. at 120° C. for 20 to 30 minutes. Pyridoxine is unstable when irradiated in aqueous solutions at pH 6.8 or above. It is readily oxidized by hydrogen peroxide and other oxidizing agents. Pyridoxine is stable in mixed vitamin preparations to the same degree as riboflavin and nicotinic acid. A one per cent aqueous solution has a pH of 3.

Rats¹⁵³ that have been deprived of vitamin B₆ over long periods of time develop fits that are epileptiform in character and show several successive stages, i.e., violent stage, helpless condition and, finally, a comatose condition. Others have reported that severe microcytic hypochromic anemia developed in puppies¹⁵⁴ and dogs¹⁵⁵ when vitamin B₆ was apparently the only missing factor in the diet. This anemia was cured by supplementing the diet with this vitamin. The symptoms



of vitamin B₆ deficiency in chicks¹⁵⁶ are slow growth, depressed appetite and inefficient utilization of food, followed in some cases by spasmodic convulsions and death.

Spies,¹⁵⁷ in 1939, showed that patients maintained on a pellagra-producing diet supplemented with nicotinic acid, vitamin B₁ and riboflavin, still showed nervousness, insomnia, irritability, abdominal pains, weakness and difficulty in walking. These symptoms were alleviated by the administration of vitamin B₆. Vitamin B₆ apparently plays a role in the cure of cheilosis, thought to be due to riboflavin deficiency.

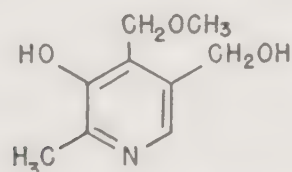
The intravenous injection of synthetic pyridoxine alleviated muscular dystrophy and Parkinson's syndrome in a number of cases. Large doses (50-100 mg.) had a sedative effect¹⁵⁸ in normal persons, epileptics and patients with deficiency diseases. It reduced or completely abolished the seizures in persons with idiopathic epilepsy.

Vitamin B₆ has been used with success for nausea and vomiting of pregnancy (30-100 mg. daily) and in the treatment of acne. In the latter case, it may play a role in the metabolism of unsaturated fatty acids or lipid substances because rats on a vitamin

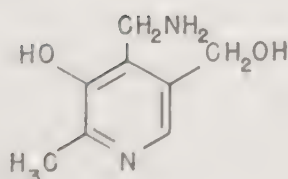
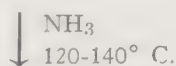
B₆ deficient diet develop enlarged fatty livers. The cheilosis associated with pellagra, sprue, celiac disease and digestive upset has been treated successfully with vitamin B₆.

Di- and triacetyl pyridoxine¹⁵⁹ are as effective as free pyridoxine in experimental animals, i.e., rats, whereas the benzoate is inactive. The methyl ether, 4-desoxypyridoxine, and 4,5-didesoxypyridoxine are much less active than pyridoxine. Although a large number of pyridine derivatives have been tested, none has shown pyridoxinelike activity.

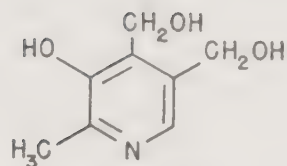
Evidence¹⁶⁰ has accumulated that pyridoxine alone is not responsible for all the activity found in naturally occurring materials. Pyridoxamine and pyridoxal have been isolated and their structures proven by syntheses.¹⁶¹ All three compounds have about equal activity for the rat, whereas there is a great variation in their activities for different micro-organisms. These compounds are rapidly inactivated¹⁶² by exposure to light, especially ultraviolet light, particularly at a pH of 7 or higher. In 0.1 N acid they are comparatively stable to light; however, pyridoxamine is destroyed fairly rapidly by direct exposure to sunlight. Oxygen, apparently, does not play a role in this light sensitivity.



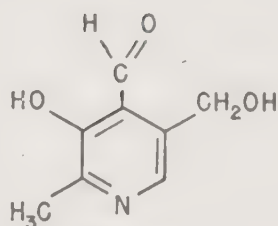
Pyridoxine Methyl Ether



Pyridoxamine



Pyridoxine



Pyridoxal

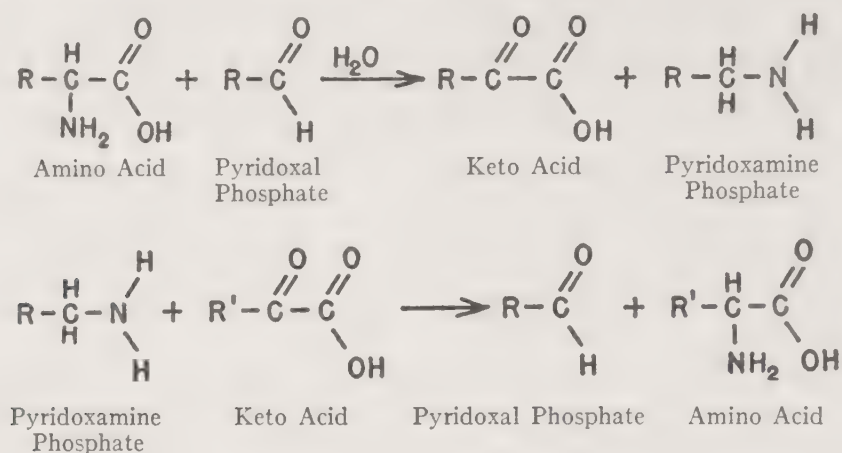
Pyridoxamine, pyridoxine and pyridoxal may function as co-transaminase in biologic transaminations.¹⁶³ It is believed that pyridoxal phosphate is the active form and that pyridoxine is a provitamin. The role of pyridoxal, as the phosphate,¹⁶⁴ is coenzymatic in the deamination or transamination of amino acids that can be depicted in part as shown in the equations at the top of page 532.

Pyridoxal phosphate (codecarboxylase) is also thought to play a role in the decarboxylation^{165, 166} of certain amino acids, such as tyrosine, lysine, arginine, ornithine, aspartic and glutamic acids. Therefore, it appears that the amount of vitamin B₆ needed by the organism is directly related to the amount of protein consumed. The extent of the above reaction varies markedly with the amino acid. Pyridoxal phosphate activates (coenzyme function) a tryptophanase that was obtained from *Escherichia coli*.¹⁶⁷

Gyorgyi¹⁶⁸ has proposed a rat unit for vitamin B₆. This is defined as the amount necessary per day to cure or prevent the typical symptoms of vitamin B₆ deficiency. This unit is equal to 10 micrograms of pyridoxine.

NICOTINIC ACID

Nicotinic Acid (Niacin) U.S.P. Nicotinic acid was first prepared in 1867 by the

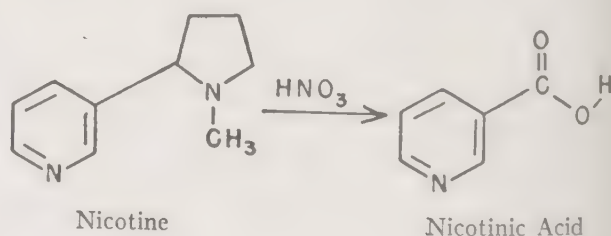


oxidation of nicotine.¹⁶⁹ It was isolated by Funk¹⁷⁰ in 1913 from yeast concentrates and about the same time by Suzuke *et al.*¹⁷¹ from rice polishings in connection with anti-neuritic studies in which it failed to have antineuritic activity. Interest in nicotinic acid and its derivatives in biologic processes lagged until Warburg and Christian¹⁷² showed that nicotinic acid amide was obtained upon the hydrolysis of a coenzyme which they isolated from red blood cells of horse blood. This coenzyme is now known as coenzyme II. Kuhn and Vetter¹⁷³ isolated nicotinic acid amide from heart muscle, and Euler *et al.*¹⁷⁴ isolated it from cozymase. These findings again focused attention upon the possible value of nicotinic acid and its amide in the nutrition of experimental animals. Some growth responses were obtained in rats and pigeons on certain diets when given these factors. However, the magnitudes were not sufficiently great enough to warrant classifying them as vitamins.

Pellagra* has been known for nearly two centuries, and the term has its origin from the Italian "*pelle agara*" meaning rough skin. By 1930, due to the excellent work of Goldberger *et al.*, pellagra in humans had been definitely established as a deficiency disease,

and the protective factor was associated with the more heat stable fraction of the vitamin B complex. Although pellagralike conditions have been produced in some experimental animals, it was finally shown that only black tongue, a dietary deficiency disease in dogs, was comparable to pellagra in humans. From liver extracts, which were efficacious in treating pellagra in humans and black tongue in dogs, nicotinic acid amide was isolated.¹⁷⁵ This compound, as well as nicotinic acid, cured black tongue in dogs. Nicotinic acid was soon tested and shown to be successful in the treatment of human pellagra.¹⁷⁶

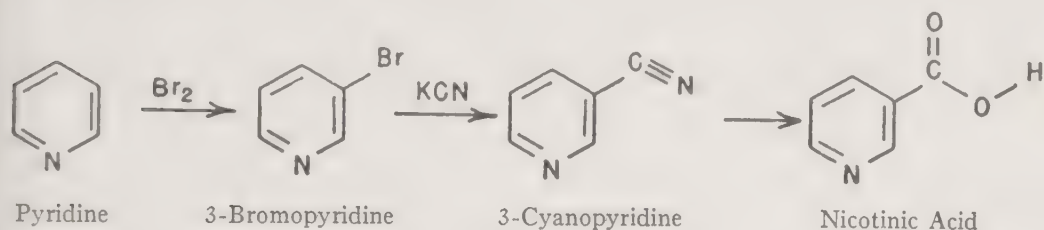
Nicotinic acid can be prepared by the oxidation of nicotine with nitric acid.¹⁷⁷ It can also be prepared by the oxidation of



other beta substituted pyridines such as β -picoline, 3-ethylpyridine, 3,3'-dipyridyl, 3-phenylpyridine, etc. The pyridine-polycarboxylic acids, with the exception of those having carboxyl groups in the four position, that have a carboxyl group in the three position undergo decarboxylation, thermal or

* Usually prevalent in people who eat certain simplified diets such as the salt pork, maize and molasses diet of the negroes and poor white people of the southern United States.

acidic, to give nicotinic acid. The pyridine-polycarboxylic acids are obtained by the oxidation of quinoline, quinaldine, etc. Nicotinic acid also can be synthesized by the following reaction.¹⁷⁸



Nicotinic acid occurs as white crystals or as a crystalline powder. It is odorless or it may have a slight odor. One gram of nicotinic acid dissolves in 60 cc. of water. It is freely soluble in boiling water, in boiling alcohol and in solutions of alkali hydroxides and carbonates, but is almost insoluble in ether. A one per cent aqueous solution has a pH of 6.

Nicotinic acid is stable under normal storage conditions. It sublimes without decomposition.

The most satisfactory chemical assay for nicotinic acid seems to be that which depends on the reaction with cyanogen bromide and aniline to produce a yellow color.¹⁷⁹ The biologic methods of importance use the cure of induced pellagra in dogs or pigs and the growth of various bacteria.

Excellent sources of nicotinic acid, its amide or its coenzymes, are pork, lamb, and beef livers, hog kidneys, brewers and bakers yeasts, pork, beef tongue, hearts, lean meats, wheat germ, peanut meal, green peas, etc. These factors are quite widely distributed in varying concentrations in animal tissues and in plants.

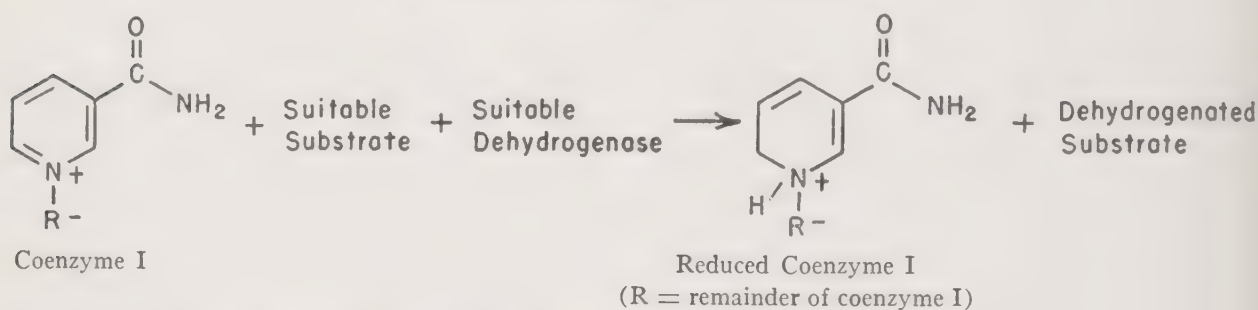
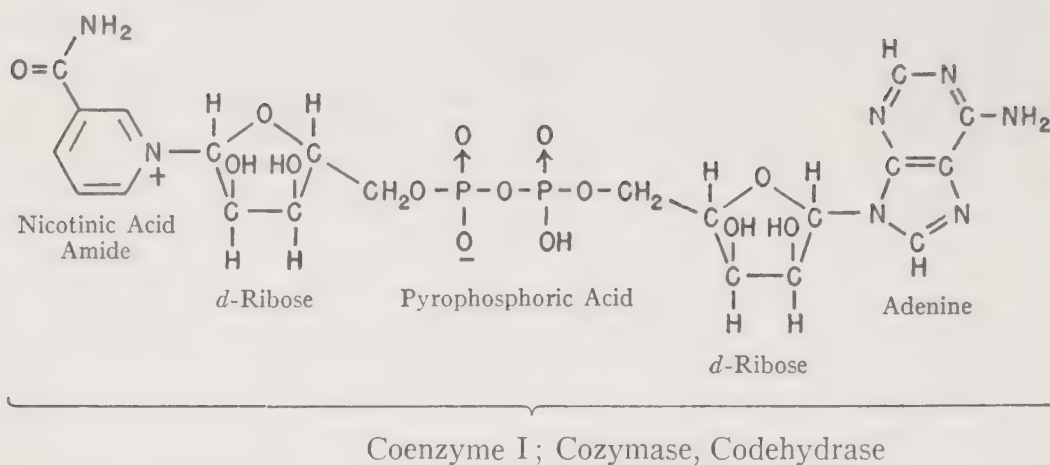
Elvehjem *et al.*¹⁸⁰ have shown that the alpha and gamma isomers of nicotinic acid, picolinic and isonicotinic acids, are completely inactive. The following compounds are also inactive, i.e., pyridine, nipecotic acid, 6-methylnicotinic acid, trigonelline, 1-methylnicotinic acid amide chloride, quino-

linic acid and β -aminopyridine. The replacement of the carboxyl groups of nicotinic acid by a sulfonic acid group or a cyano group leads to inactive compounds.

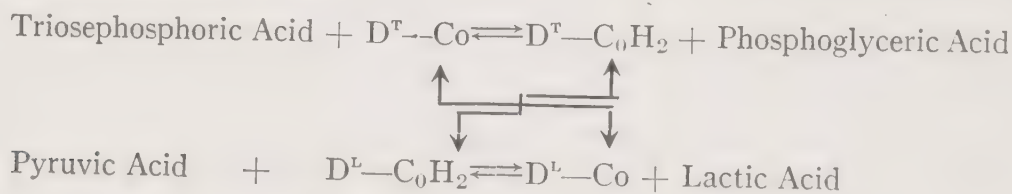
It appears probable that, in addition to nicotine acid and its amide, only those compounds that are capable of oxidation or hydrolytic conversion to these substances in the body possess anti-black tongue activity. Examples of these are ethyl nicotinate, nicotinic acid N-methylamide, nicotinic acid N-diethylamide, beta picoline and nicotinuric acid. Both the mono- and the 2,3-dicarboxylic acid derivatives of pyrazine show some activity in pellagras; they have one-tenth the activity of nicotinic acid in the treatment of black tongue in dogs. Thiazole-5-carboxylic acid also shows some biologic activity.

Nicotinic acid has been shown to exist as the amide as a component of coenzymes I and II. The latter differs from the former only in that it contains an additional molecule of phosphoric acid. Nevertheless, they possess remarkable specificity in relation to the dehydrogenases* with which they will function. In most cases, a substance (together with its dehydrogenase) will react with one of the coenzymes but not with the other. The nicotinic acid portion of these coenzymes acts as hydrogen acceptors and donators in a number of biologic oxidation and reduction systems in the metabolism of carbohydrates, amino acids and fats.

* Lactic acid, malic acid, glycerophosphoric acid, glutamic acid, glucose, Robison ester, etc.



Coenzymes I and II accept hydrogen or are reduced in the presence of certain specific dehydrogenases and suitable substrates such as alcohol, acetaldehyde, hexose phosphates, phosphoglyceric aldehyde, isocitrate, oxalacetate, etc. These coenzymes act as hydrogen transporting agents in aerobic systems and will reduce riboflavin phosphate in the presence of a suitable enzyme. They will also act as reducing agents in anaerobic systems, and many of the above dehydrogenations are reversible. The function of coenzyme I, for example, in an anaerobic system can be depicted as follows :



Key: D^T = Triose dehydrogenase
D^L = Lactic Acid Dehydrogenase
Co = Coenzyme I
CoH₂ = Reduced or Dihydrocoenzyme I

Studies on nutrition have indicated that coenzyme I (cozymase) could completely replace nicotinic acid amide and be more effective on a mole for mole basis. The ad-

ministration of nicotinic acid has been shown almost invariably to increase the level of cozymase in the blood of both normal persons and pellagrins. The cozymase content of liver and muscle rises and falls with the nicotinic acid intake. Evidence is accumulating that indicates a direct relationship between carbohydrate metabolism, insulin and nicotinic acid (in the form of coenzymes I and II). This is because pellagra signs and a deficiency of cozymase of the blood have been shown to be associated with diabetics.

Pellagra in humans is manifested by very complex symptoms.¹⁷⁶ In brief, these are characterized by: (1) A typical dermatitis may develop anywhere, usually following a bilaterally symmetrical pattern, and may be accompanied by pigmentation. (2) A characteristic glossitis appears, and in the early

similar characteristics and similar biologic activities. However, the ability of these substances to promote the growth of microorganisms such as *Lactobacillus casei* or *Streptococcus lactis* (the two most commonly used test organisms) vary with the source and method of treatment.¹⁸³ For example: (1) yeast and liver yield a factor that is active for *Lactobacillus casei*, but may have little to one-half the activity for *Streptococcus lactis* R.; (2) liver, yeast and spinach yield a factor (folic acid or vitamin B_c) that is equally active for both organisms; (3) a fermentation culture of *Corynebacterium* yielded a factor called "fermentation *Lactobacillus casei* factor" that was active for *Lactobacillus casei* but had little activity for *Streptococcus lactis* R.; (4) *Rhizopus Nigricans* yielded a factor (rhizopterin¹⁸⁴) that was active only for *Streptococcus lactis* R. The first factor, when incubated with a rat liver enzyme or fresh chick liver, showed a marked increase in activity for *Streptococcus lactis* R. If β -pyracin* was added to the above incubation mixture, twice as much activity was obtained. Furthermore, yeast that showed a low folic acid content when incubated with fresh liver gave a yeast with a high folic acid content. A crystalline vitamin B_c,¹⁸⁵ (folic acid) obtained from liver that had anti-anemic properties for the chick† was microbiologically active for *Streptococcus faecalis*. Yeast concentrates yielded a vitamin B_c conjugate in crystalline form that was active as a chick anti-anemic factor and which became microbiologically active only after it was subjected to treatment with vitamin B_c, conjugase, from hog kidney, hog liver, intestine¹⁸⁶ or almond

* 2-Methyl-3-hydroxy-4-carboxy-5-hydroxymethylpyridine.

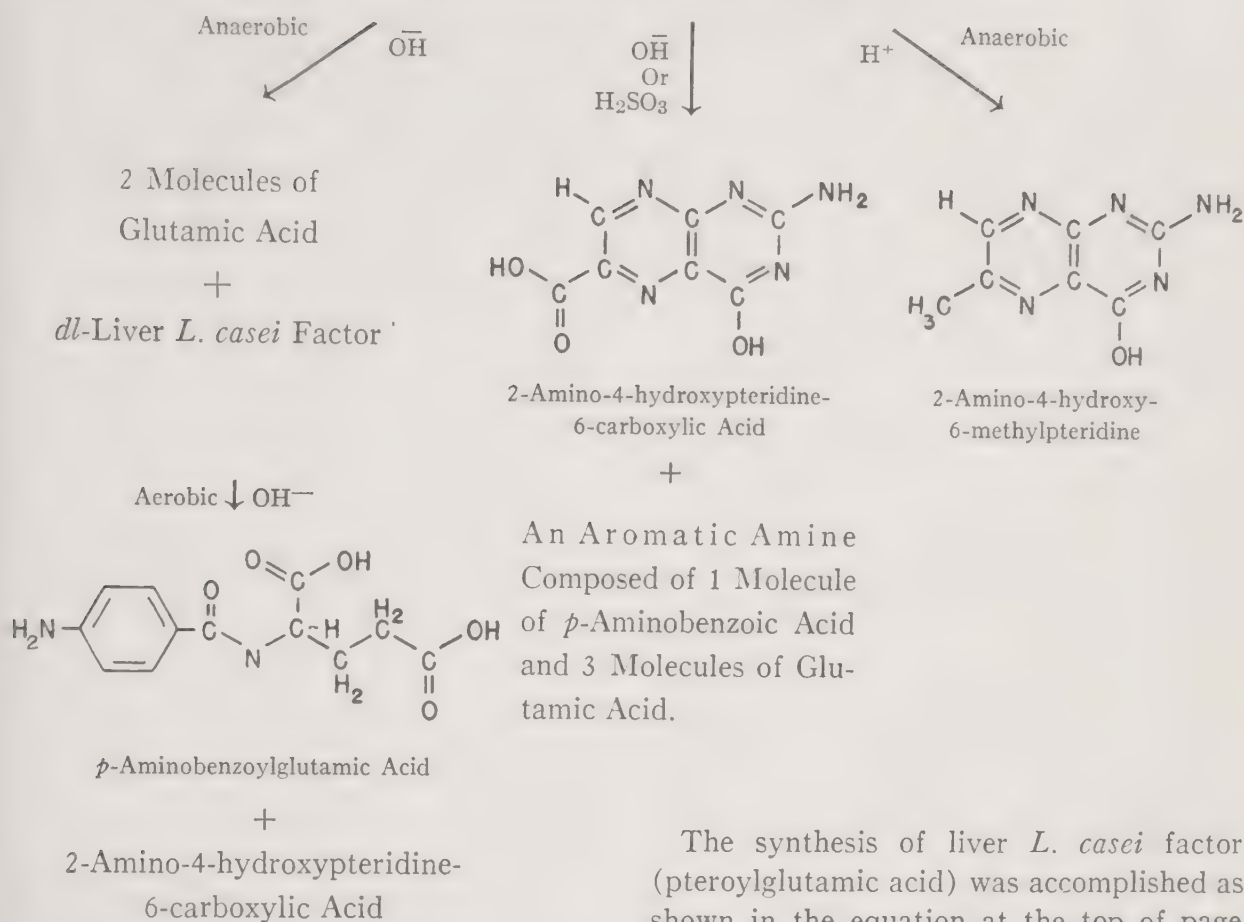
† This nutritional anemia in chicks is characterized by retarded growth; decrease in hematocrit, hemoglobin and red blood cell count; reduction in the leucocytes and thrombocytes. Chicks make a suitable experimental subject because absorption from the lower intestine is at a minimal and, therefore, bacterial syntheses would not present a problem as it does in rats.

meal. Therefore, folic acid can also exist partially preformed or in the form of a conjugate not utilizable as such by all test organisms. It is also possible that folic acid itself may not be the only essential factor of this nature and that very minor changes in structure may produce great changes in activity for various organisms.

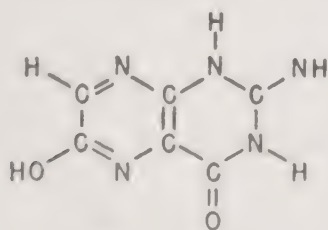
A considerable number of compounds¹⁸⁷ have been tested for folic acid activity, and one compound, thymine, replaces folic acid if present in sufficient quantity (1 γ per cc. of culture medium). Activity was manifested by a considerable number of other compounds that show a slight activity at very high concentrations, i.e., 10 γ per cc. of culture medium. Among these are hypoxanthine, guanidine, alloxan, allantoin and xanthopterin. When xanthopterin was digested with fresh rat liver, the folic acid content was markedly increased. Xanthopterin was found to be five times as effective as folic acid when tested for anti-anemia activity in trout.

In 1931, Wills¹⁸⁸ showed that yeast was curative for the pregnancy macrocytic anemia which occurs commonly in India. Wills and Bilimoria, in 1932,¹⁸⁹ showed that monkeys, when placed upon a diet comparable to that of the natives of India, developed an anemia, leucopenia, granulocytopenia, necroses of the gums and diarrhea. Day *et al.*, in 1935, obtained the same results and named the deficiency factor vitamin M.¹⁹⁰ This condition can be cured by yeast, liver extract, grass extract or a folic acid preparation. A similar condition can be induced in rats only when succinylsulfathiazole is also added to the diet. This may be explained because it is believed intestinal bacteria can serve as a source of folic acid as well as some other nutritional factors. Folic acid and xanthopterin are able to counteract the effect of succinylsulfathiazole in rats. Folic acid stimulates the growth of rats.

The degradation of the fermentation *L. casei* factor can be depicted schematically as follows.¹⁹¹

Fermentation of *L. casei* Factor

The pteridine portion of the molecule is unique, whereas the *p*-aminobenzoic and glutamic acids are simple and well known. Hopkins, as early as 1889,¹⁹² recognized that the pigments of butterfly wings were purine derivatives. Wieland,¹⁹³ in 1925, proposed the generic term pterins for the colored and colorless pigments that occur in butterfly wings. In 1935, Bavarian children collected 250,000 cabbage butterflies, from which sufficient pigment was obtained to elucidate the constitution of xanthopterin,* which has been shown to be as follows:



Xanthopterin

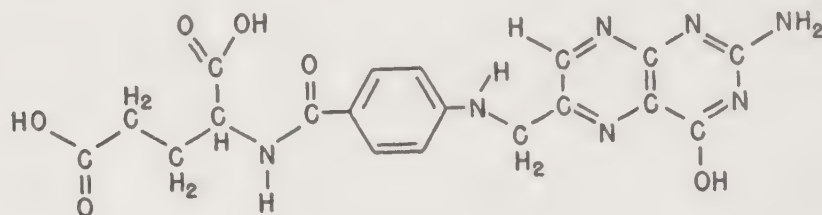
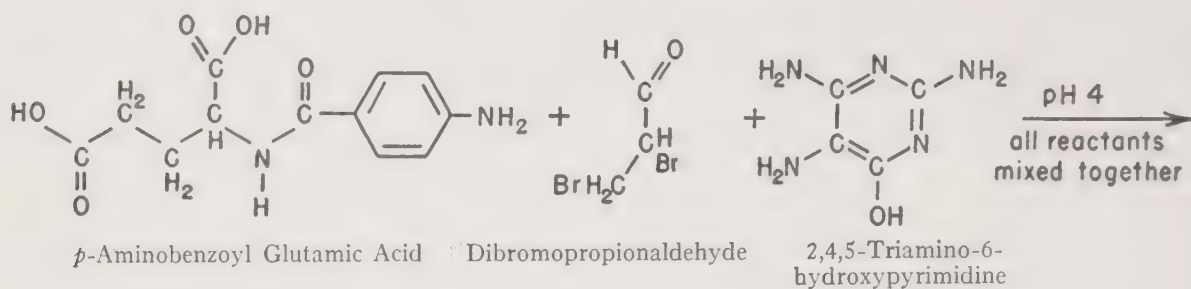
* Found in human urine.

The synthesis of liver *L. casei* factor (pteroylglutamic acid) was accomplished as shown in the equation at the top of page 538.¹⁹⁴

The fermentation† *L. casei* factor appeared to contain three glutamic acid residues. Both factors have the same pteridine nucleus attached to *p*-aminobenzoic acid. Since a chemical name was too long for general usage, a name for the basic nucleus indicating its pterine nature was proposed. Thus, the name "Pteroylglutamic Acid" was proposed for the liver *L. casei* factor. The basic structure was proposed as "Pteric Acid" and chemically is 4 [$\leftarrow$ (2-amino-4-hydroxy-6-pteridyl) methyl $\rightarrow$ amino] benzoic acid; it was synthesized in the same way as pteroylglutamic acid. Pteric acid and rhizopterin are active only for *Streptococcus lactis* R.

Vitamin B₉ conjugate is pteroylhexaglu-

† Fermentation product of a diphthoid bacterium that was more easily isolated than other related factors and, therefore, employed to a large extent for proof of structure work.



N { 4 [(2-Amino-4-hydroxy-6-pteridyl) methyl > amino] benzoyl } glutamic Acid

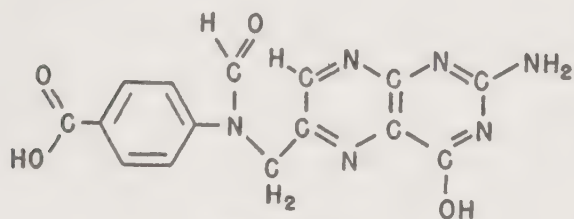
Liver *L. casei* Factor

Pteroylglutamic Acid

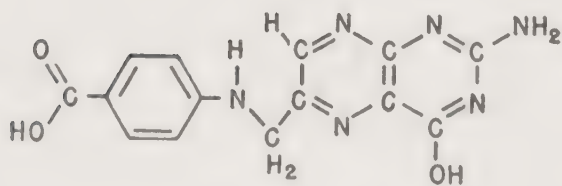
Folic Acid*

* Folic Acid (Pteridyl-para-aminobenzoyl glutamic acid) N.N.R.

tamylglutamic acid, and the enzyme vitamin B₆ conjugase is a peptidase and since it does not hydrolyze vitamin B₆ conjugate methyl ester, it can be identified as a pteroylglutamylcarboxypeptidase. Most of the pteroylglutamic acid in food exists in a conjugated form.



Rhizopterin



Pterioic Acid

Folic acid occurs as a yellow powder that is only slightly soluble in water (1 mg. per 100 cc.). It is insoluble in the common or-

ganic solvents. The sodium salt is soluble (1:66) in water.

Aqueous solutions of folic acid or its sodium salt are stable to oxygen of the air, even upon prolonged standing. These solutions can be sterilized by autoclaving at a pressure of 15 pounds in the usual manner. Folic acid in the dry state and in very dilute solutions is readily decomposed by sunlight or ultraviolet light. Although folic acid is unstable in acid solutions, particularly below a pH of 6, the presence of liver extracts has a stabilizing effect at lower pH levels than are otherwise possible. Iron salts do not materially affect the stability of folic acid solutions. The water-soluble vitamins that have a deleterious effect on folic acid are listed in their descending order of effectiveness as follows: riboflavin, thiamine hydrochloride, ascorbic acid, niacinamide, pantothenic acid and pyridoxine. This deleterious effect can be overcome to a considerable degree by the inclusion of approximately 70 per cent of sugars in the mixture.

Folic acid in foods is more readily destroyed by cooking than are the other water-

soluble vitamins. These losses range from 46 per cent in halibut to 95 per cent in pork chops and from 69 per cent in cauliflower to 97 per cent in carrots.

Pteroylaspartic acid¹⁹⁵ inhibits the growth of chicks, *Lactobacillus casei* and *Streptococcus faecalis* and, therefore, is an antagonist for pteroylglutamic acid. It does not inhibit *Escherichia coli* or growth of rats. A number of 2,4-diaminopterins¹⁹⁶ inhibit the growth of *Strept. faecalis* and *Lactobacillus casei*, which require preformed folic acid, and *Lactobacillus arabinosus*, which synthesizes its own needs of this factor.

In the presence of an adequate supply of preformed pteroylglutamic acid, enterococci and certain lactobacilli were relatively insensitive to the sulfonamides. *p*-Aminobenzoic acid showed a competitive type of antagonism. Therefore, it can be concluded that in these experiments, the primary point of inhibition was the syntheses of pteroylglutamic acid and related compounds via *p*-aminobenzoic acid. *p*-Aminobenzoyl-*l*-glutamic acid was 8 to 10 times as active on a molar basis as *p*-aminobenzoic acid in antagonizing the inhibition of *Lactobacillus arabinosus* by sulfanilamide. Sulfonamides inhibit the growth of those bacteria that synthesize their own supply of folic acid but not those that cannot synthesize this factor but require it as a preformed substance. Some purines and thymine are also products of enzyme systems in which *p*-aminobenzoic acid functions. These compounds when added to the media in some cases render the bacteria insensitive to sulfonamides.¹⁹⁷

Folic acid is active orally or parenterally in chicks and prevents the following: retarded growth, decrease in the hematocrit, hemoglobin, red blood cell count and reduction of leucocytes and thrombocytes. Folic acid activity in chicks and hens is enhanced by the simultaneous administration of α -pyracin (2-methyl-3-hydroxy-4-hydroxy-methyl-5-carboxypyridine) or β -pyracin (2-methyl-3-hydroxy-4-carboxy-5-hydroxy-methylpyridine).

Some pernicious anemia patients¹⁹⁸ in relapse fail to utilize the conjugate, whereas the normal individual appears to be able to utilize this form. The free vitamin is excreted in the urine of the latter after administration of the conjugate, whereas in the former this does not occur. Spies¹⁹⁹ believes that folic acid (vitamin B₁₂) is liberated by enzymes more readily in some of the anemias than in others. Relatively large amounts of folic acid are required in eliciting a favorable hemopoietic response, as compared with the small quantity contained in equally effective liver extract.

Pteroylglutamic acid readily can be reduced²⁰⁰ to take up two hydrogens and reoxidized again and, therefore, the possibility exists that it can serve in biologic oxidation-reduction reactions.

In macrocytic anemias, folic acid duplicates the effects of liver therapy, i.e., an increase in reticulocytes, red and white cells, platelets, normoblasts and hemoglobin. The decrease of bone marrow megaloblasts and the return of vigor and appetite are the physical manifestations. Folic acid performs a specific function in the maturation of the various cells of the bone marrow and has other obvious profound effects on the human body.

In contrast to the excellent hematopoietic activity in pernicious anemia, several reports indicate the failure of therapy with pteroyl glutamic acid to arrest the progress or to prevent the subsequent development of neurologic symptoms and signs. Neurologic manifestations may develop rapidly many weeks after the blood values have been restored to and maintained at normal levels.

Teropterin (Sodium Pteroyl Triglutamate, Sterile Solution) is synonymous with the sodium salt of the fermentation *Bactobacillus casei* factor. It is reported to be of value in the treatment of malignant cancer.

Folic acid can be administered orally or parenterally in the treatment of a number of macrocytic anemias, including sprue,²⁰¹

macrocytic anemias of pregnancy and those of gastro-intestinal origin and the macrocytic anemias associated with pellagra and similar states.²⁰²

Five to six times as much folic acid is excreted in sweat as in the urine in humans; this amounts to 0.0038 to 0.0238 mg. per day.

The average dose is 5 to 10 mg.

VITAMIN B₁₂

Vitamin B₁₂ was first isolated from liver. This isolation was traced by its growth stimulating action for *Lactobacillus lactis* Dorner. It occurs as small red needles that have an indefinite melting point. The compound is organic and apparently contains some cobalt. It occurs in liver in about one part in one million.

Vitamin B₁₂ is very effective in the treatment of Addisonian pernicious anemia. Single doses as small as 3 to 6 micrograms have produced in patients a prompt increase in the circulating reticulocytes, the red cells and the hemoglobin.

p-AMINO BENZOIC ACID

In 1940,²⁰³ it was shown that *p*-aminobenzoic acid was an essential factor for the growth of bacteria. It was also observed that it possessed an antisulfanilamide activity²⁰⁴ in vitro experiments. These facts directed attention to the possibility that *p*-aminobenzoic acid might have vitamin properties. Rats²⁰⁵ which had developed a definite graying of fur when maintained on the basal ration G H—I, could be restored to normal by the administration of *p*-aminobenzoic acid. *p*-Aminobenzoic acid was also shown to be an essential factor in the maintenance of life and growth of the chick.²⁰⁵ Since these original developments in this field, various claims²⁰⁶ have been made for the chromatrichial value of *p*-aminobenzoic acid in rats, mice, chicks, minks and humans. However, in the case of experimental achromotrichia in rats, it has been shown that in sufficiently large doses, pantothenic acid will effect a cure, and that biotin elim-

inates the scattered gray hairs "stippling" remaining after the pantothenic acid treatment. The problem of nutritional achromotrichia is a complex one that may involve several vitamin or vitaminlike factors and is complicated by the synthesis and absorption from the intestinal tract of a number of factors produced by bacteria.

p-Aminobenzoic acid is a white crystalline substance that occurs widely distributed over the plant and animal kingdom. It occurs both free and combined²⁰⁷ and has been isolated²⁰⁸ from yeast, in which it is a natural constituent.

p-Aminobenzoic acid is thought to play a role in melanin formation, influence or catalyze tyrosine activity.²⁰⁹ It inhibits oxidative destruction of adrenaline and stilbestrol, counteracts the graying of fur attributable to hydroquinone in cats and mice, exhibits antisulfanilamide activity and detoxifies the toxic effects of carbarsone and other pentavalent phenylarsonates.²¹⁰

p-Aminobenzoic acid, when given either parenterally or in the diet to experimental animals, will protect them against otherwise fatal infections of epidemic or murine typhus, Rocky Mountain spotted fever and tsutsugamushi disease.²¹¹ These diseases have been treated clinically with most encouraging results by maintaining blood levels of 10 to 20 milligrams per cent for Rocky Mountain spotted fever and tsutsugamushi diseases. The mode of action of *p*-aminobenzoic acid in the treatment of the above diseases appears to be rickettsiostatic rather than rickettsiocidal, and the immunity mechanisms of the host finally overcome the infection.

p-Aminobenzoic acid appears to function as a coenzyme in the conversion of certain precursors to purines.²¹² It is also a component of the folic acid molecule (see folic acid).

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29

Proteins and Amino Acids

AMINO ACIDS

PROTEIN HYDROLYSATES

PROTEINS

ENZYMES

INSULIN

BLOOD PRODUCTS

Proteins, from the Greek meaning primary or first importance, make up the majority of organic compounds in animal tissues and fluids and, next to carbohydrates, in those of plants as well. They are produced exclusively by living organisms and most of them are very sensitive to change by physical stimuli and by reagents. Indeed, very little is known about the properties of natural proteins because they are undoubtedly altered chemically during any process of isolation. What can be described here are only the characteristics of substances that have been extracted from living or dead organisms, although some few observations can be made on mixtures of compounds during the living processes. It cannot be emphasized too strongly that any discussion of classification or structure must be merely for the isolated compounds and may apply only in part to those compounds that actually take part in the processes of metabolism in plants and animals.

That the natural proteins are important in these operations is so well-known as to be almost axiomatic. They occur universally in all cells and in all extracellular matter, and one could justifiably conclude that they are absolutely necessary for the life of plants and animals. They were the first substances that were known to be essential in the food of man and other animals and are just as

necessary in the life processes of plants, although there they can be synthesized from the elements and water. The multitude of vital changes that go on continuously in the living organism are apparently governed entirely by specialized proteins called enzymes, and naturally there could be no life without these. Furthermore, it becomes increasingly evident that states of immunity and detoxication are brought about through the instrumentality of proteins, and that certain of the vitamins, if not all, are effective only in combination with particular proteins. Indeed, we can almost conclude that no vital process could take place without them, and it was suggested years ago that living bodies could be defined as that portion of matter in which protein metabolism takes place.

In contradistinction to carbohydrates and fats, the other two groups that make up the bulk of foods, proteins contain not only carbon, hydrogen, and oxygen, but also nitrogen, sulfur, phosphorus and other elements. However, nitrogen occurs in all of them, whereas sulfur and phosphorus may be entirely absent in particular compounds, and only sulfur is found with nitrogen in the so-called simple proteins. Although carbon, hydrogen and oxygen are fundamental, just as they are in most living matter, the universally distinctive element in proteins is nitrogen. It might be termed the essence of life,

notwithstanding that it often is spoken of as "azote" meaning "without life," but in another sense. The complexity of proteins is so great that it is practically impossible to distinguish between compounds on the basis of elementary analysis. The percentage would be found about as follows: carbon 40-55, hydrogen 5-8, oxygen 12-32, nitrogen 12-32, sulfur 0-3, phosphorus 0-4, but the majority have a much closer range, such as 15-17 per cent of nitrogen. This last value is so near the true situation that analytical chemists who work with foods have almost universally adopted the method of finding the per cent of protein by multiplying that

this process yield only well known amino acids; hence, these are called simple proteins. Others first split off from the simple ones other substances that are not considered proteins and may not even contain nitrogen. These are called conjugated proteins, and the radicals of the nonprotein portion are designated as the prosthetic (=added on) groups. When the simple compounds are hydrolyzed further, they furnish substances that are still highly complicated but have different properties, and these are classed as derived proteins.

The simple or true proteins are placed into seven classes on the basis of solubilities and

TABLE 55. SIMPLE (TRUE) PROTEINS

CLASS	CHARACTERISTICS	OCCURRENCE
ALBUMINS	Soluble in water, coagulable by heat and reagents	Egg albumin, lactalbumin, serum albumin, leucosin of wheat, legumelin of legumes
GLOBULINS	Insoluble in water, soluble in dilute salt solution, coagulable	Edestin of plants, vitelline of egg, serum globulin, lactoglobulin, amandin of almonds, myosin of muscles
PROLAMINES	Insoluble in water or alcohol, soluble in 60-80% alcohol, not coagulable	Found only in plants, e.g., gliadin of wheat, hordein of barley, zein of corn and secalin of rye
GLUTELINS	Soluble only in dilute acids or bases, coagulable	Found only in plants, e.g., glutenin of wheat and oryzenin of rice
PROTAMINES	Soluble in water or ammonia, strongly alkaline, not coagulable	Found only in the sperm of fish, e.g., salmine from salmon
HISTONES	Soluble in water, but not in ammonia, predominantly basic, not coagulable	Globin of hemoglobin, nucleohistone from nucleoprotein
ALBUMINOIDS	Insoluble in all solvents	In keratin of hair, nails and feathers; collagen of connective tissue; chondrin of cartilage; fibroin of silk and spongin of sponges

for nitrogen by 6.25 ($100 \div 16$), on the basis that the quantity of this element averages 16 per cent. Phytovitellin, one of the purest of proteins that have been isolated, has carbon 52.43, hydrogen 7.12, oxygen 21.80, nitrogen 18.10 and sulfur 0.55 per cent.

The classification that has been adopted the world over is based only on physical and chemical properties. In recent years, scientists have learned a great deal about possible structure and consequently, have shown a tendency to divide the proteins on a different basis, about which more will be noted later, but the present arrangement is convenient in many respects. The most fundamental property of all is that of easy hydrolysis to simpler compounds, and some of them by

of coagulability by heat or reagents. When hydrolyzed, all of them give a mixture of amino acids only. Table 55 shows these characteristics and gives representative compounds.

AMINO ACIDS

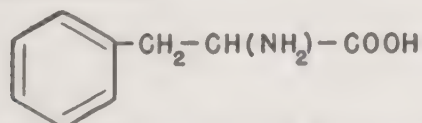
Amino acids are organic carboxylic acids containing a free or substituted amino ($-\text{NH}_2$) group. This definition would include an almost unlimited variety of organic structures; however, the common usage of the term amino acids refers to the α -amino carboxylic acids that are obtained by the hydrolysis of proteins. Aminoacetic acid ($\text{NH}_2-\text{CH}_2-\text{COOH}$) is the simplest of the amino acids produced by hydrolysis of proteins, and all others may be considered as

substitution products of it because the recognized ones are of the alpha variety, $R-CH(NH_2)-COOH$, and their formulas are obtained by simply changing the character of R. In the prolines, however, there is cyclization between R and NH_2 . It will be noted from this formula that all of the amino acids contain an asymmetric carbon atom, except aminoacetic acid, and would be expected to exist naturally in an optically active form. Although at least 46 have been isolated from natural materials, only half of these have been proved to come from proteins, and two of those that have are from the thyroid gland. The following list of the recognized ones gives, in addition to other data, the common names and structure of R, and the student is advised to become well acquainted with both.

Glycine (aminoacetic acid, glycoll), NH_2-CH_2-COOH , was isolated by Braconnot from gelatin in 1820 and synthesized by Perkin in 1858. It melts at about $230^\circ C.$, with decomposition, and is soluble in about 4 parts of cold water.

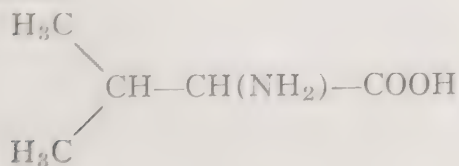
Alanine, $CH_3-CH(NH_2)-COOH$, was isolated in 1888 by Weyl from silk fibroin, but had previously been synthesized by Strecker in 1850, and was resolved by Fischer in 1899. The natural acid melts at about $297^\circ C.$ with decomposition, is soluble in about 5 parts of cold water and has a rotation of about $+3.5^\circ$.

Phenylalanine.



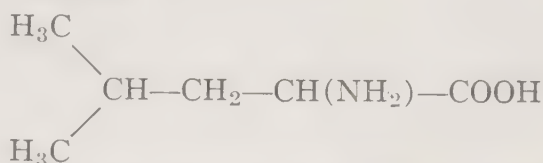
Phenylalanine was obtained from egg albumin by Schulze and Barbieri in 1881. It was synthesized by Posen in 1879 and by Erlenmeyer and Lipp in 1882, and was later resolved by Fischer and Mouneyrat in 1900. It melts at about $283^\circ C.$, is soluble in about 35 parts of cold water and has a rotation of about -35° .

Valine.



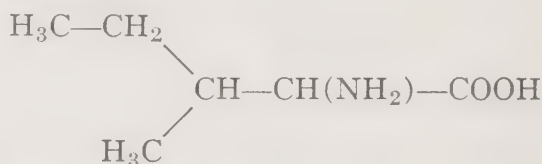
Valine was obtained from the pancreas by Gorup-Besanez in 1856 and from a pure protein by Fischer in 1901. It was synthesized by Clark and Fittig in 1866 and resolved by Fischer in 1906. It melts at about $315^\circ C.$, is soluble in about 50 parts of cold water and has a rotation of about $+6.5^\circ$.

Leucine.



Leucine was isolated from cheese by Proust in 1818, but was not known to be derived from protein until Braconnot obtained it from wool in 1820. It was first made in the laboratory by Schulze and Likiernik in 1891 and was resolved by Fischer and Warburg in 1905. It melts at about $295^\circ C.$ with decomposition, is soluble in about 45 parts of cold water and has a rotation of about -10.5° .

Isoleucine.



Isoleucine was obtained from casein by Fischer in 1901, synthesized by Bouveault and Loquin in 1905 and resolved by Loquin in 1907. It melts at about $280^\circ C.$, is soluble in about 26 parts of cold water and has a rotation of about $+9.5^\circ$.

Norleucine, $CH_3-CH_2-CH_2-CH_2-CH(NH_2)-COOH$, was made in the laboratory by Schulze and Likiernik in 1893, eight years before it was isolated from brain tissue by Thudichum and resolved by Fischer and Hagenbach in 1901. It melts at $301^\circ C.$ after a partial sublimation at $275-280^\circ$, is soluble in about 63 parts of cold water and has a rotation of about $+6.3^\circ$.

Threonine.

$CH_3-CHOH-CH(NH_2)-COOH$
Threonine was undoubtedly obtained by Gortner and Hoffman in 1925 and by Schryver and Buston in 1926, but was only exactly characterized by Rose and his colleagues in 1935. It was first synthesized by Carter in 1935, and was resolved two years

later by West and Carter. It melts at 285° C. (Carter 252°), is soluble in water and has a rotation of about -6.8° .

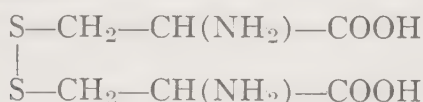
Serine. $\text{CH}_2\text{OH}-\text{CH}(\text{NH}_2)-\text{COOH}$, was discovered by Cramer in 1865 as a product of hydrolysis from silk. It was synthesized by Fischer and Leuchs in 1902 and resolved by Fischer and Jacobs in 1906. It melts with decomposition at 228° C., is easily soluble in water and has a rotation of about -6.8° .

Cysteine.



Cysteine was obtained from egg albumin by Embden in 1901 and even earlier by Baumann, but only recently has it been given recognition as a product from proteins. It was made in the laboratory by Erlenmeyer and Stopp in 1904, but the synthetic product has not been resolved. It is easily soluble in water and is levorotatory.

Cystine.



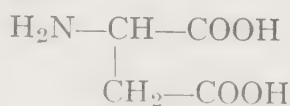
Cystine, first obtained from gall stones in 1810 by Wollaston, was not recognized as a product from proteins until Mörner obtained it from horn in 1899. It was synthesized by Erlenmeyer in 1903 and resolved by Fischer and Rasche in 1908. It decomposes at 258-261° C., is very difficultly soluble in water (1:8,840) and has a rotation in hydrochloric acid of about -225° .

Methionine.



Methionine was first isolated from casein by Mueller in 1921. It was synthesized by Barger and Coyne in 1928 and resolved by Windus and Marvel in 1931. It melts at 283° C., is soluble in cold water and has a rotation of about -7° .

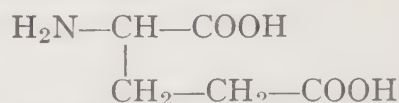
Aspartic acid.



Aspartic acid was isolated from asparagus and marshmallow in 1827 by Plisson, but it was not known to come from a protein until Ritthausen obtained it from legumin and

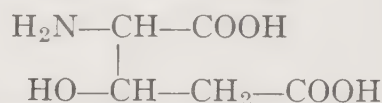
conglutin in 1868. It was made from the ammonium salts of malic, maleic or fumaric acid in 1850 by Dessaignes and was later (1887) synthesized by Puitti. It was resolved by Fischer in 1899. It melts at about 270° C., dissolves in about 250 parts of cold water or 20 parts of boiling water and has a rotation of $+4.36^\circ$ at 20° C. and -0.6° at 80° C.

Glutamic acid.



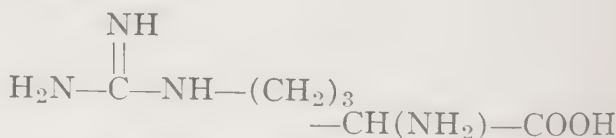
Glutamic acid was isolated from gluten by Ritthausen in 1866, synthesized in 1890 by Wolff and resolved by Fischer in 1899. It melts when heated rapidly at 206° C., is soluble in about 100 parts of cold water and has a rotation of about $+12^\circ$.

Hydroxy glutamic acid.



Hydroxy glutamic acid was first obtained from casein by Dakin in 1918, who also synthesized it in 1919, but it has not yet been resolved. It is easily soluble in water and has a slight dextro rotation.

Arginine.



Arginine was obtained by Schulze and Steiger in 1886 from lupine and by Hedin in 1895 from horn. It was synthesized by Schulze and Winterstein in 1899. The product has been converted to the levo form by the action of arginase, but it has not been resolved. It decomposes at about 207° C., is easily soluble in water and has a rotation of about $+11.4^\circ$.

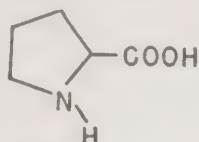
Lysine.



Lysine was first obtained from casein in 1889 by Drechsel, but it was not obtained in the crystalline state until 1928 (Vickery and Leavenworth). It was synthesized in 1902 by Fischer and Weigert and was resolved by Berg in 1936. It melts at 224° C., is easily

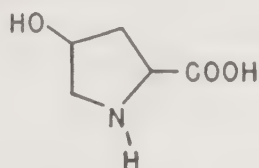
soluble in water and has a rotation in hydrochloric acid of $+15.3^\circ$.

Proline.



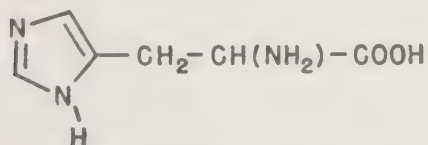
Proline was isolated by Fischer in 1901, but had previously been synthesized by Willstätter in 1900. It was resolved by Fischer and Zemplén in 1909. It melts at $206-209^\circ\text{C}$., is easily soluble in water and has a rotation of about -80° .

Hydroxyproline.



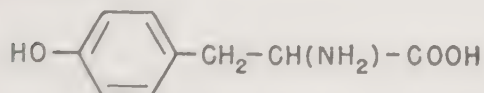
Hydroxyproline was obtained by Fischer from gelatin in 1902. It was synthesized by Leuchs in 1905 and later resolved by the latter. It melts at $260-270^\circ\text{C}$., is easily soluble in water and has a rotation of about -80° .

Histidine.



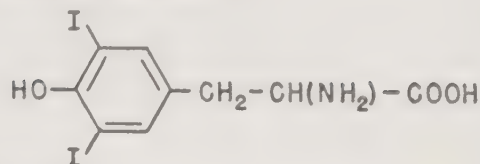
Histidine was obtained almost simultaneously by Kossel and by Hedin in 1896 from sturine and from horn; it was synthesized and resolved by Pyman in 1911. It melts at about 277°C ., is freely soluble in water and has a rotation of about -40° .

Tyrosine.



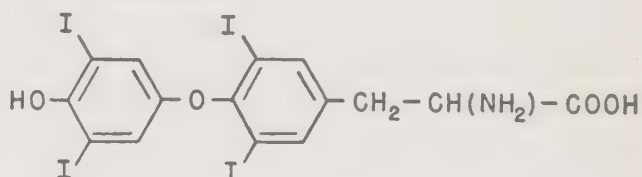
Tyrosine was first isolated from casein in 1846 by Liebig. It was synthesized by Erlenmeyer and Lipp in 1883 and resolved by Fischer in 1899. It decomposes at $290-299^\circ\text{C}$., is only slightly soluble in water (1:2,490) and has a rotation in hydrochloric acid of about -8.5° .

Iodogorgoic acid.



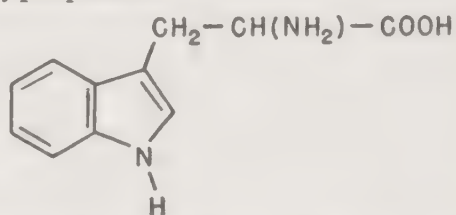
Iodogorgoic acid, obtained from coral by Drechsel in 1896, was made in the laboratory by Wheeler and Jamieson in 1905. It has been resolved only by the hydrolysis of thyroglobulin. It melts at about 213°C . with decomposition, is soluble in about 350 parts of cold water and has a slight levo rotation, although it is dextro in either ammonia or hydrochloride acid.

Thyroxine.



Thyroxine is only obtained from proteins of the thyroid gland, where it was found by Kendall in 1919. It was synthesized by Harington and Barger in 1926 and resolved by Harington in 1928. It melts with decomposition at 297°C ., is almost insoluble in water and has a slight levo rotation in hydrochloric acid.

Tryptophane.



Tryptophane had been observed by means of color reactions as early as 1825, but it was not actually separated from a protein until this was accomplished by Hopkins and Cole in 1902. Ellinger and Flamand performed the synthesis in 1907, and the product was resolved by Berg in 1933. The natural compound melts at about 289°C ., is slightly soluble in cold water but more easily soluble in hot water and has a rotation of about -32° .

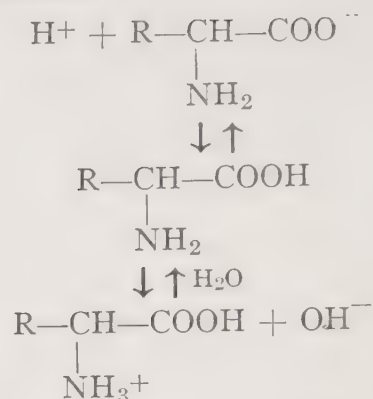
The amino acids are colorless, crystalline solids that dissolve in varying degrees in water; the notably less soluble compounds are cystine, tyrosine, thyroxine and trypto-

phane. Except proline, they are mostly insoluble in alcohol, and all of them are insoluble in ether. From hydrolytic mixtures, they sometimes can be separated by differences of solubility in various solvents. Most of them have a high melting point, which is consistent with their structure as salts, and usually decompose at the same time. All of them except glycine are optically active, but the direction and amount of rotation varies considerably with the solvent, the pH, the temperature and other factors. Five of them have two asymmetric carbon atoms and, therefore, should furnish four active compounds each, except cystine in which the two atoms are equivalent and which must furnish a meso derivative. Some of those for which data are available undergo the Walden inversion when dissolved in acids; in other words, the rotation of the salts is opposite in direction to that of the free base.

They are designated, according to structure around the asymmetric carbon atom, by the prefixes *d*- and *l*-, just as are the carbohydrates and other compounds. The literature abounds with the use of these symbols for *dextro* and *levo*, as they were originally designed, and the suggestion of such an eminent chemist as Emil Fischer that they be used for configuration instead was unfortunate, to say the least. Nevertheless, the use of *d*- and *l*- to indicate structure has met with popular approval, in spite of the resulting confusion. In the case of amino acids, this confusion is most evident since many writers obviously use *d*- and *l*- to indicate rotation. There are good reasons to think that all of them are of the *l*- type in nature; hence, they should be so designated or no letter at all should be used if this is not known. For example, natural histidine is of the *l*- type and has *levo* rotation, and it should be labelled *l*(—)-histidine, while alanine should be *l*(+)-alanine and glutamic acid should be *l*(+)-glutamic acid.

The amino acids are obviously both acids and bases and would be expected to have no reaction towards some indicators. They are typical examples of amphoteric electrolytes or ampholytes, just as are aminophenols and

sulfanilic acid.



If the theoretical assumption that both dissociations are equal in amount is made, they not only should form unstable salts with either acids or bases, as they do, but also in neutral solution they should give $\text{R}-\text{CH}-\text{COO}^-$ the so-called "Zwitterion"

$\begin{array}{c} \text{NH}_3^+ \\ | \\ \text{R}-\text{CH}-\text{COO}^- \end{array}$ or "amphion," an internally compensated salt as is Na^+Cl^- . The high melting point, typical of true salts, corroborates this view. Such a compound would be equally attracted to the poles of an electrolytic apparatus and could not migrate in either direction. However, as could be foretold, the two dissociations are not equal, and the amounts will vary with each particular compound. But they can be made to be equal by adjusting the pH of a solution until no migration takes place in either direction; the pH at this stage is known as the isoelectric point. Because the amphion is less soluble than any other form of the compound, the solubility is lowest at the isoelectric point, and this is true also of the more complex proteins. The approximate points of a few are: glycine, 6.1; alanine, 6.1; aspartic acid, 3.0; arginine, 10.8; histidine, 7.6; isoleucine, 6.0; glutamic acid, 3.2; proline, 6.3.

It will have been noted that some of the amino acids have more basic than acidic groups and vice versa. Most of them have but one carboxyl and one amino or two each as in cystine. Tyrosine, hydroxyproline, iodo-gorgoic acid and thyroxine also have enolic (phenolic) groups that are potentially acid, while aspartic and the glutamic acids have extra carboxyl groups. Arginine, tryptophane, lysine and histidine have additional

TABLE 56. YIELD OF AMINO ACIDS FROM REPRESENTATIVE PROTEINS

	ALBUMIN (MILK)	GLOBULIN (SERUM)	(AMOUNTS GIVEN IN PER CENT)				
			PROLAMIN (ZEIN)	GLUTELIN (GLUTENIN)	PROTAMINE (SALMINE)	HISTONE (GLOBIN)	ALBUMINOID (KERATIN)
Alanine	2.5	2.2	9.8	4.7	...	...	4.4
Arginine	3.2	5.2	1.8	4.7	...	3.6	7.8
Aspartic Acid	9.3	2.5	1.8	0.9	...	8.9	2.3
Cystine and Cysteine	4.0	1.1	0.8	0.1	...	0.6	13.1
Glutamic Acid	12.9	8.0	31.0	25.4	...	6.3	12.9
Glycine	0.4	3.5	0.0	0.9	...	...	0.6
Histidine	1.5	0.9	0.8	1.8	...	7.6	0.7
Hydroxyglutamic Acid	10.0	...	2.5	1.8	...	...	...
Leucine and Isoleucine	14.0	18.5	25.0	6.0	...	8.0	11.5
Lysine	8.4	6.2	0.0	1.9	...	8.1	2.3
Methionine	2.3	...	2.3	...	87.4	...	...
Phenylalanine	1.2	3.8	7.6	2.0	...	...	...
Proline	4.0	2.8	9.0	4.2	11.0	...	4.4
Serine	1.8	...	1.0	0.7	7.8	...	2.9
Tryptophane	2.7	2.4	0.2	1.7	...	1.3	1.8
Tyrosine	1.9	6.7	5.8	4.3	...	3.2	4.8
Valine	3.3	...	1.0	0.2	4.3	...	0.6

amino groups and are predominantly basic. Tryptophane, however, is more like the majority because the cyclic nitrogen is very weakly basic.

Other chemical properties of amino acids are sometimes of great importance, although they are what might be expected of amino and carboxyl compounds. The formation of esters with alcohols is utilized to make separations from hydrolysates of proteins. Most of them (not the prolines) have free primary amino groups which can be transformed to hydroxyl by nitrous acid, a property utilized in the Van Slyke method for determining the free amino in proteins by measuring the nitrogen that is liberated. Formaldehyde will mask the amino group by combining with it, thus affording a means for determining free carboxyl by "formol titration" (Sörensen). Acylating agents also will mask the basic properties, and the carboxyl groups then can be converted to acid halides. They can be decarboxylated by heating with barium hydroxide to produce primary amines, or they can be dehydrated to form either cyclic derivatives or peptides (q.v.).

Isolation of the acids from products of hydrolysis is a tedious and time-consuming process in general, although it is still the most economical source for some of the amino acids. The first one, cystine, was found by Wollaston in gall stones in 1810,

but was not recognized as a derivative of proteins for nearly a century. Although Proust found leucine in cheese in 1818, it was really Braconnot who laid the foundation for isolation studies in 1820 when he obtained leucine from wool and muscle and glycine from gelatin. The others have followed gradually, at first by accident because of crude methods, later more rapidly when refinements decreased the labor involved. A partial view of the history can be obtained when it is noted that eight of the 24 compounds have been proven since 1900, that the last essential one (threonine) was not found until 1925, that there is now some evidence for aminobutyric acid and that several others have been isolated but not confirmed. The chief difficulties lie in the facts that the chemical and physical properties are so much alike, that they cannot be distilled without decomposition, and that they are very sensitive to reagents. However, useful precipitating agents have been found for some, distinctive solvents for a few and various other effective procedures in most cases; as examples, the prolines can be precipitated by Reinecke's salt, and 3,4-dichlorobenzenesulfonic acid is useful to extract histidine in the same way. Other reactions have been helpful, including the discovery by Fischer that esters can be made and fractionally distilled.

The determination of amounts from a

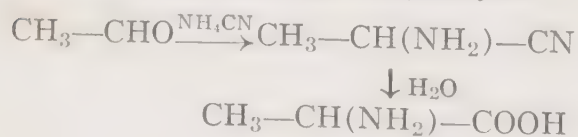
given protein is an even more difficult task for most of them, and the figures as given in the literature must be accepted with some reservation. Van Slyke has devised an ingenious method based on the reaction of primary amines with nitrous acid, precipitation with phosphotungstic acid, determination of free ammonia by distillation and the Kjeldahl method, but the results can be only approximate at best. For some, special reagents have been found to give colors that can be interpreted quantitatively, such as *p*-dimethylaminobenzaldehyde for tryptophane, but in the presence of so much extraneous material, it is doubtful how close the result can be to the correct value.

The amino acids are obtained in different amounts from various proteins, often not at all from a particular one. As illustrative, Table 56 shows the percentage yield from a representative of each class of simple proteins. The absence of a figure in any case does not mean that none is obtained, but simply that no one has yet isolated that acid and estimated its amount. Left out of the table are norleucine, hydroxyproline and threonine, for which few data can be found, as well as iodogorgonic acid and thyroxine, which are only found in the hydrolysates of proteins from the thyroid gland.

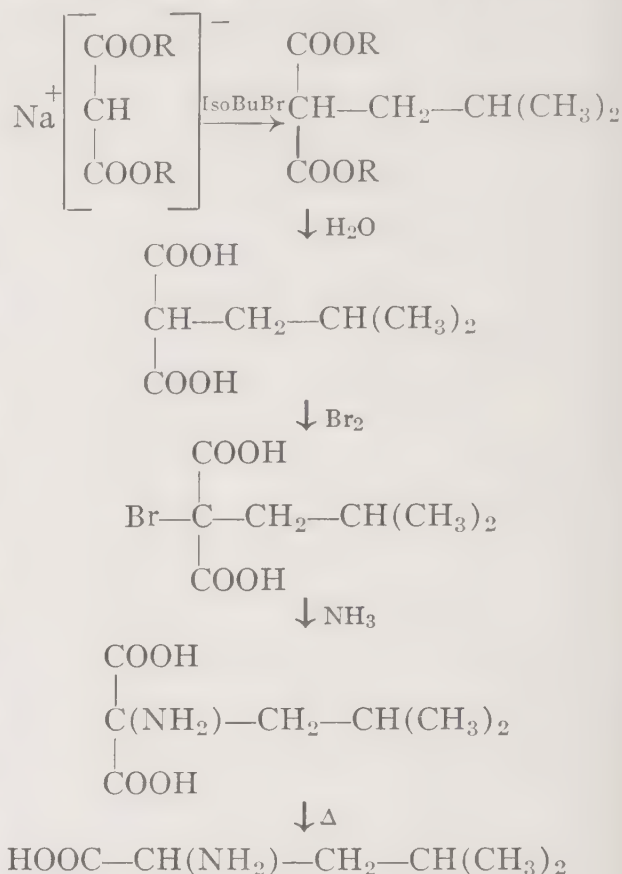
All of the amino acids have been produced in the laboratory, often for commercial purposes, but by a variety of methods that cannot be given in detail here. For a complete review, the student is referred to special texts.¹ The simplest method, which involves reaction between ammonia and the requisite halide, was utilized for glycine in 1857, but it gives a poor yield unless a large excess of ammonia is employed, and is otherwise unsatisfactory.



The cyanohydrin method, first used by Strecker for alanine in 1850, depends on the addition of hydrocyanic acid and ammonia to aldehydes and subsequent hydrolysis.



The malonic ester synthesis, first employed for leucine by Fischer in 1906, can be satisfactory if the necessary halide is available.



Modifications of this method, using amino-malonic ester, a combination with the phthalimide process of Gabriel, and the intermediate formation of azides have been used successfully. Other methods involve condensation of aldehydes with hydantoin, thiohydantoin, hippuric acid, diketopiperazine or rhodanine, and special ones for individual acids.

For practical purposes, it is at present considered more economical to get supplies of some amino acids by isolation rather than by synthesis. This is particularly true of leucine, cystine, cysteine, glutamic acid, arginine, tyrosine, the prolines and tryptophane. On the other hand, improved methods of production frequently have resulted in ample supplies of some at continually reduced prices. Thus, methionine, which formerly sold at almost fabulous prices, can now be purchased at less than 3 cents per gram.

The reconstruction of natural proteins from amino acids, which would constitute the reversal of hydrolysis, is still in the realm

of theory. Emil Fischer, proceeding on the basis that the union is an amide one by splitting out water between amino and carboxyl groups, made a series of compounds that he called peptides. Using glycine alone, glycylglycine,

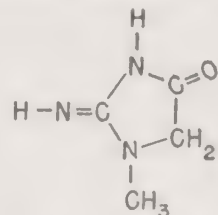


a dipeptide, could be produced. While the difficulties of manipulation for producing higher peptides seem almost insurmountable, since drastic treatment by reagents to effect condensation can so readily lead to decomposition of previous unions, yet he was able to link up 3 molecules of leucine with as many as 15 molecules of glycine. The polypeptide so obtained was somewhat similar to certain derived proteins and could be hydrolyzed by some proteolytic enzymes. Whether or not the theory of peptide linkage is a correct one cannot be settled at present, but the prevailing opinion is that Fischer's experiments were on the right track. If so, the proteins are made up of long peptide chains made by removal of water, undoubtedly complicated in some by cross-linkages to produce more or less globular molecules, in others a stretchable or fibrous structure by folding. X-ray diffraction studies of fibrous albuminoids have partly confirmed the fact that the unitary distances are according to calculations.

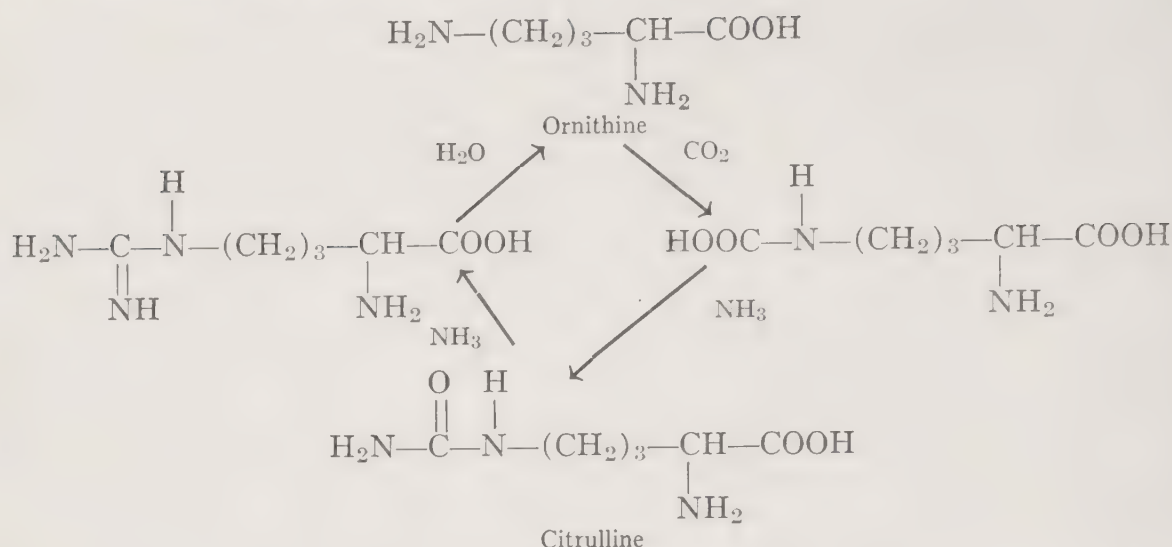
The nutritional significance of the amino acids has but recently been appreciated. It has long been known that proteins are essential to life and that some of them are more important than others for certain of the metabolic processes. It also was recognized that all of them are mostly, if not entirely, hydrolyzed to the individual amino acids during digestion. It is but a short step from these facts to conclude that the significant problem in metabolism is, not what proteins are ingested, but what is the nature of the amino acids that can be obtained from them. It is now apparent that some foods do not produce optimum results, and may not even maintain life, merely because they fail to provide certain vital products. By means of experiments using purified amino acids on

animals, it has been determined that ten of these must be furnished in the food in order to sustain life and maintain growth, and these are called the essential amino acids. Others may be just as vital to the metabolism, but in some way can be synthesized in the body when required. The ten are arginine, leucine, lysine, isoleucine, histidine, methionine, phenylalanine, threonine, tyrosine and valine. Further experiments have shown that all of these except histidine and arginine are essential in human beings, but the tests have been too limited as yet to say that others are not equally vital. Apparently the human body is able to synthesize enough histidine and arginine. Recommended daily intake levels for the eight amino acids that are essential in man are: *l*-tryptophane, 0.5 Gm.; *l*-phenylalanine, 2.2 Gm.; *l*-lysine, 1.6 Gm.; *l*-threonine, 1.0 Gm.; *l*-valine, 1.6 Gm.; *l*-leucine, 2.2 Gm.; *l*-isoleucine, 1.4 Gm.; and methionine, 2.2 Gm.

During metabolic processes, amino acids other than the 24 listed are encountered; these must have been manufactured in the body, since they do not come from the proteins of food as far as is known. Creatine, $\text{NH}_2\text{—C(=NH)—N(CH}_3\text{)—CH}_2\text{—COOH}$, is found almost entirely combined with phosphoric acid in the muscles, in which form it is intimately concerned with carbohydrate metabolism. When muscular effort is exerted, some of the creatine is set free and excreted as the anhydride creatinine, which is elim-



inated by the kidneys. Creatine apparently is manufactured from arginine and glycine and usually is in adequate amounts, because any extra creatine that is ingested is excreted immediately. Ornithine and citrulline seem intimately bound up with the manufacture of urea and are evidently formed from arginine in the process, which may be represented diagrammatically as follows:



Pantothenic acid is generally considered one of the vitamins. (See Chap. 28.)

Besides these, other amino acids have been found in hydrolysates from various mixtures, but none has as yet been confirmed as an actual derivative of proteins. Dibromotyrosine unquestionably was separated from certain corals, and aminobutyric acid has been obtained from several sources by a number of workers. In 1904, the isolation of diaminoadipic, diaminoglutaric, dihydroxydiaminosuberic, hydroxyaminosuccinic, caseanic ($\text{C}_9\text{H}_{16}\text{N}_2\text{O}_6$) and caseinic ($\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5$) acids from casein was reported, but these have never been confirmed. In 1925 and 1926, the isolation of hydroxylysine from gelatin and hydroxyvaline and protoctine ($\text{C}_8\text{H}_{15}\text{N}_3\text{O}_3$) from oats was reported. Canaline (2-amino-4-hydroxybutyric acid) and canavanine (its guanidyl ether) have been obtained from soy and jack beans. Hydroxytryptophane was apparently separated in 1907, but this was later found to be a mixture. The same laboratory reported norvaline (hydroxyvaleric acid derivative) from casein and from globin. β -alanine has been obtained from carnosine, from anserine and from pantothenic acid. Djenkolic acid, a higher homologue of cystine, comes from djenkol nuts and also urine, while homocysteine and homocystine have been reported. Thiol-histidine (mercapto in position 2) has been found in the blood, while 3,4-dihydroxyphenylalanine (dopa) was obtained from peas and beans and dihydroxypyrrrolealanine from gelatin. Some of these 22 compounds

may later be added to the list of those known to come from specific proteins.

Aminoacetic Acid (Glycocoll, Glycine) N.F. "contains not less than 18.4 per cent and not more than 18.8 per cent of N, corresponding to not less than 98.5 per cent of $\text{C}_2\text{H}_5\text{O}_2\text{N}$." It occurs as a white, odorless, crystalline powder, having a sweetish taste. It is insoluble in alcohol but soluble in water (1:4) to make a solution that is acid to litmus paper. With ferric chloride, it gives a deep wine color which disappears with an excess of hydrochloric acid and reappears on adding an excess of ammonia, and with phenol and sodium hypochlorite, it yields a blue color. Besides occurring in the hydrolysates of proteins, it is found in the bile in combination with cholic acid. It usually is prepared by any one of several patented processes, such as the reaction of chloroacetic acid with ammonia or ammonium carbonate. It is synthesized in the body in adequate amounts and is not one of the essential group.

It was introduced into therapy for the treatment of progressive muscular dystrophy or myasthenia gravis. This was based on the ill-founded assumption that it is concerned vitally in the formation of creatine, which is so important in muscular metabolism. There have been a great many favorable reports on its use in such conditions, and in poliomyelitis and Addison's disease, but the general consensus seems to be that it is of little value. It is given in doses of 30 grams three to four times a day.

OFFICIAL OCCURRENCE N.F.	PER CENT AMINOACETIC ACID
Aminoacetic Acid Elixir....	12.1 to 14.2

Histidine Monohydrochloride N.F., a salt of histidine, "contains not less than 21.5 per cent and not more than 22.2 per cent of N, calculated on the moisture-free basis, corresponding to not less than 98 per cent of $C_6H_9N_3O_2 \cdot HCl$." It consists of small, glistening, colorless crystals that are odorless, possess a salty taste, and dissolve in water (1:8) to produce a solution that is acid to litmus. The specific rotation in about 2.5 per cent solution is $+9.3^\circ$ to $+11.2^\circ$, although histidine itself is levorotatory. With bromine, it gives a yellow color which becomes much darker on heating and precipitates amorphous particles. Histidine occurs naturally in many proteins and in the urine of pregnant women; it is most conveniently prepared from blood corpuscles by hydrolysis and precipitation with mercuric sulfate. It can be synthesized and resolved to the *levo* form from its combination with *dextrotartaric* acid.

Histidine was suggested in the treatment of gastric ulcer because of a theory that deficiency of the compound causes and maintains the ulcer. Many physicians have observed amelioration of symptoms after a series of injections but, in carefully controlled clinical experiments, it has been found that the results are variable and unreliable, and that, in general, there is no effect on the ulcer itself. A certain percentage of patients have experienced untoward reactions, such as hemorrhage.

The official dose is 0.2 gram, and this is administered intramuscularly each day for a 20 to 30 day period.

Glutamic Acid occurs in the hydrolysates of protein and also free in tissues and blood plasma (6-10 mg. per 100 cc.), in eggs and in many plants. It has been used in place of glycine in the treatment of muscular dystrophies with rather unpromising results. It is also combined (8-20 grams) with anti-convulsants for the petit mal attacks of epilepsy, a use which appears to depend on change in pH of the urine. The hydrochloride, which releases the acid readily, has been recommended under a variety of names (Acidogen, Acidulin, Achlor, Gastruloric, Glutan, Glutasin, Hydrionic, Muriamic) for furnishing acid to the stomach in the achlorhydria of pernicious anemia and other conditions.

The average dose is 0.3 Gm.

Methionine is a white, crystalline powder with a slight, characteristic odor and is soluble in water (1:35). In recent years it has been produced in ever increasing quantities and at considerably reduced cost. The human body needs proteins that furnish it in order to prevent pathologic effects; one of these is the sign of liver injury, which can be counteracted by administration of the acid or proteins that provide it. A second role is its function in the synthesis of choline, cystine, lecithin and probably creatine. Deficiency not only limits growth in rats, but also inhibits progression of tumors.

In therapy, methionine has been employed in the treatment of liver injuries caused by poisons such as carbon tetrachloride, chloroform, arsenic and trinitrotoluene. While many physicians are enthusiastic about its value under such circumstances, this has not yet been satisfactorily established. It is also administered to treat eclampsia and shock, probably on the basis of protecting the liver. The dose of the racemic compound is 0.5 to 3.0 grams daily, the smaller amount being for prophylaxis.

Cysteine is easily produced from cystine by reduction and equally as readily oxidizes to the latter. It is probably found in many proteins, especially in keratin of hair and nails. Normal growth requires one of the two compounds in the body, in part at least to produce taurine for the bile, glutathione and keratin, and to detoxify certain poisons. However, it can apparently be synthesized by the metabolism from methionine and is not essential in the food. It has been used in solution for applying to ulcers and slow healing wounds and to treat certain kinds of tumors; it was once recommended as a remedy in Addison's disease.

Thyroxin U.S.P. "contains, when dried over sulfuric acid for 18 hours, not less than 64 per cent of iodine as an integral part of the thyroxin molecule." It occurs as white, needlelike, odorless, tasteless crystals that are affected by light, are insoluble in water or alcohol, but are soluble in alcohol in the presence of mineral acids or alkalies. When an acidified alcoholic solution is treated with sodium nitrite and warmed, it develops a yellow color which is changed to pink on adding an excess of ammonia.

Thyroxin has essentially the same physiologic action as the thyroid gland, although it probably does not represent the entire activity. It is capable of more exact dosage and, after special preparation in alkaline solution, can be given by injection. In therapeutics, it is employed but seldom because the same effects can be gained by the cheaper and more efficient official form of thyroid gland or iodides.

The official dose is 0.5 milligram, and it is usually administered in a maximum dose of 1 milligram.

Thyroid U.S.P. is the cleaned, dried and powdered thyroid gland, previously deprived of connective tissue and fat, and obtained from domesticated animals that are used for food by man. It "contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination." The gland is intimately concerned with basal metabolism, the regulation of growth and development and other processes. Absence or lack of functioning leads to a condition called cretinism, if congenital, or myxedema in the adult; the main observable effects are retardation of growth and mental development, dermal edema, rough and dry hair and anemia. Simple or colloid goiter is caused by defective functioning, while toxic goiter usually gives symptoms of hyperthyroidism.

The administration of thyroid or thyroxin gives effects only after a day or two, but these continue for varying periods up to three weeks. There is an increase in basal metabolism, which is directly proportional to the dose, giving enhanced excretion of nitrogen and consumption of oxygen, and

a loss in weight in spite of increased appetite. Toxic manifestations follow from amounts very little more than therapeutic doses; they are restlessness, nervousness, headache, insomnia, muscular weakness, indefinite pains, sweating, tachycardia, tremors, glycosuria and emaciation.

Thyroid and thyroxin are considered specific in myxedema and cretinism, but they are not usually cures and must be continued indefinitely. They also can be used to raise the metabolism, as for example, in obesity, but the dangers of overdosage are very great, and frequent determination of the basal metabolic rate is essential. They sometimes are used to reduce simple goiter, but the iodides generally will accomplish the same purpose at a fraction of the cost. The dose of thyroid is 0.06 gram.

The other individual amino acids are as yet of no importance in therapy. Iodogorgonic acid has been administered under the title of Organon in Grave's disease (dose of 0.1 gram daily), but there is no indication that better effects are obtained than with the same amount of inorganic iodides. Tryptophane deficiency in animals causes cataract, corneal vascularization, loss of weight, greasy hair, alopecia and nervousness; these are not the same as the similar effects caused by deficiency of vitamins. Increased amounts of tyrosine (10 per cent) in the diet of rats causes keratitis, swelling of the feet and degeneration of the pancreas, the kidneys and the arterioles.

PROTEIN HYDROLYSATES

Exhaustive hydrolysis of proteins (proteolysis) ultimately results in the liberation of the constituent free amino acids. Incomplete proteolysis yields a mixture composed principally of free amino acids with small amounts of dipeptides, polypeptides, and peptones that is recognized as protein hydrolysate. The hydrolysis can be accomplished by alkalies, but this results in destruction of methionine, cystine and perhaps others, and in racemization of most. It also can be performed by acids, a method which has the advantage of leaving no peptides but which results in loss of trypto-

phane. Proteolytic enzymes are also available; these give excellent products, but they are comparatively slow and the process is never complete. Peptides with relatively small molecules are unobjectionable, but the product is not suitable if it contains comparatively large molecules from the substrate.

The products are employed to supplement the diet in cases of protein deficiencies and have a limited, but as yet undetermined, value in the treatment of disease. The lack of adequate protein may result from a number of conditions, but it is not always easy to diagnose. It may arise from insufficient intake, normally about 1 gram or less per kilogram of weight; from temporarily increased demands, as in pregnancy; from impaired digestion or absorption in the intestinal tract due to diseased conditions; from poor assimilation because of diseases of the liver or other organs; from increased decomposition or loss of amino acids or proteins during diseases, such as fevers, leukemia or hemorrhage or after operations, burns, fractures or shock. Under the last set of conditions, the loss of protein may be very large, as much as 150 grams per day. There seems little need for any more therapy than an adequately selected diet in the majority of cases, but when there is an allergy towards proteins, the hydrolysates may be indicated orally, while the parenteral presentation may be useful in some of the other conditions.² Untoward reactions have been observed after injection, such as nausea, vomiting, fever, vasodilation, abdominal pain, twitching and convulsions, as well as edema at the site of the injection, phlebitis and thrombosis. These generally can be prevented by injecting the material more slowly.

Amigen N.N.R. is obtained from casein by pancreatic digestion. It contains all of the essential amino acids, as well as some peptides. It is given in a dose of 1.3 grams (1 gram of casein) orally per kilogram and provides 33 calories for every 9 grams. Parenterally, it may be administered in the form of a 5 per cent solution in 5 per cent dextrose or as a 10 per cent solution in water. The contents of containers must be used immedi-

ately upon opening or must be discarded.

Elamine Lyophilized N.N.R. is a similar product prepared from casein by acid digestion.

Solution Parenamine N.N.R. is a 15 per cent solution of hydrolysate from casein containing essentially amino acids. It contains added racemic tryptophane to make up for that lost by decomposition.

Protolysate N.N.R. is prepared from casein by digestion with fish ceca and is designed for oral administration.

PROTEINS

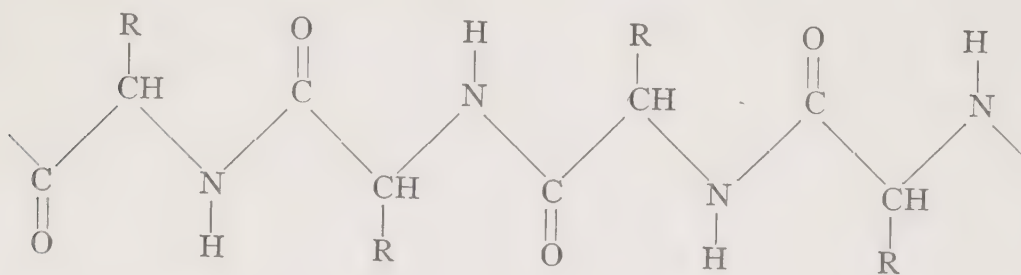
The isolation of individual proteins is not difficult, but purification represents an almost unsolved problem. The molecular weights are tremendously high, even for the simplest proteins, and they show a strong tendency to combine with each other and with substances of different classes. Nevertheless, the physical and chemical properties are more or less variable, even among those proteins of the same general class, and usually enough differences can be found to make a separation, while crystalloids can be eliminated by electrodialysis. The crude material, however, often clings so tenaciously to gross impurities that nothing short of decomposition seems successful in removing them. Even those that have been crystallized are far from being pure materials; indeed, it is doubtful if any protein has ever been obtained in a high degree of purity.

As criteria for determining this purity, unusual methods are employed. The proteins have no melting points, and the molecular weights are so high that an elementary analysis means very little because any experimental error in analysis is magnified many times. One of the methods is to obtain solubility curves, plotting the amount dissolved against the quantity used. Another is the determination of isoelectric point by electrolytic means and the changed point during purification. Still another is observation of the sharpness of meniscus between supernatant liquid and protein solution in the ultracentrifuge and in electrophoresis. Judged upon such principles, several of those compounds that have been separated in re-

cent years are fairly satisfactory in degree of purity.

Determination of the molecular weight must rest on different procedures than those usually employed. One way that has been attempted can be used whenever there is present an element such as iron whose amount can easily be estimated in usual quantitative methods. Thus, hemoglobin has a minimum molecular weight of 16,670 if there is only one atom of iron per molecule. As another example, the amount of sulfur can be related to the percentage of methionine and cystine and again calculated to a minimal value. The most profitable method, however, has been with the ultracentrifuge, where the rate of sedimentation is determined by special optical systems at up to 80,000 rotations per minute. According to the values found for the common proteins, the minimum weight for simple compounds such as albumin or pepsin is about 35,000, between that value and 500,000 for the usual compounds, but may run up to several million in such substances as the virus of tobacco mosaic.

As has been mentioned before, the molecular structure is largely a matter of theory, although physical methods have thrown considerable light on it in recent years. The amino acids apparently are united together in amide or peptide linkages into long chains.



These may be cross-linked at various points of cysteine side chains through extra carboxyl or amino groups or by transference of hydrogen, and there may be even actual cyclization into rings containing the piperazine pattern. Chemists have shown a tendency in recent years to divide proteins into fibrous ones, mostly those of the albuminoid type, and the globular ones that are more or less

soluble. The fibrous proteins, in which the neutral amino acids are predominant, consist only of simple chains, although they frequently may be folded (α) or stretched out (β). In the globular proteins, which are much more complicated, the molecular shape tends to be spherical and much interwoven. Most of the information on which these decisions are based has been obtained from x-ray diffraction studies, including actual measurements, of unit spacings.

In working with protein material, a number of more or less characteristic color tests have been formulated. The biuret test, given by all of them, consists of the formation of a pink to purple color when the proteins are mixed with an excess of alkali and a small amount of copper sulfate. In Millon's reaction, dependent on the presence of tyrosine, the majority of the compounds produce a brick-red color or precipitate when boiled with mercuric nitrate in an excess of nitric acid. The Hopkins-Cole reaction, in which the indole group of tryptophane is necessary, produces a violet zone when the solution is mixed with a salt of glyoxylic acid and stratified over sulfuric acid. The xanthoproteic test, given by practically all proteins and dependent upon an aromatic ring, produces a brilliant orange zone when a solution in concentrated nitric acid is stratified under

ammonia. The ninhydrin reaction, given by all proteins, produces a blue color when the material is boiled with triketohydrindene hydrate (ninhydrin), and this color is intensified by the presence of pyridine.

Other general reactions of proteins are often important. Alcohol usually will precipitate them, but this will not be complete

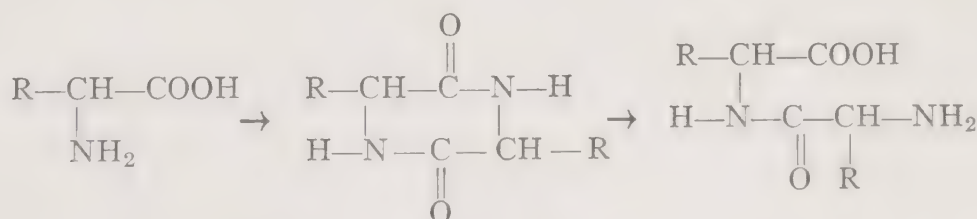
unless they are at the isoelectric point. Almost all so-called alkaloidal reagents will precipitate proteins in slightly acid solution, as will also mercuric chloride, silver nitrate, copper sulfate and other salts of heavy metals. Often the products will redissolve in excess, which may be due partially to acidity of the solutions. Relatively small amounts of mineral acids tend to give precipitates, but larger quantities usually redissolve these, probably because of incipient hydrolysis. Coagulation of some proteins is caused by heat, but the temperature of this denaturing process depends on pH and the presence of various ions. They also may be denatured by heating in acid or alkaline solution without coagulation to form metaproteins or by exposure to reagents or ultraviolet light for extended periods. The most striking feature of protein reactions is their ability to combine with each other and with practically any other class of organic compounds, such as vitamins, pigments, carbohydrates, lipids or hormones.

The known conjugated proteins are placed in several groups according to the nature of the prosthetic group. The nucleoproteins, which have previously been noted (Chap. 19), furnish a histone and nucleic acids. The phosphoproteins contain phosphoric acid and, hence, are predominantly acid in character; casein of milk and ovovitellin of eggs are notable illustrations. Glycoproteins, which furnish carbohydrates as the prosthetic group, include mucin of saliva and other secretions and mucoid of connective

representatives are found in the blood of animals. Lipoproteins yield fatty acids and have not been greatly studied.

The derived proteins are formed by hydrolysis or other denaturation of the simple ones. Minor changes in the molecule produce the class referred to as primary proteins (metaproteins and coagulated products). Proteoses represent a secondary group resulting from more extensive hydrolysis by acids, or, more especially, by proteolytic enzymes. They are not coagulable but are soluble in water; some of them are precipitated by half saturation with ammonium sulfate and by nitric or picric acids. The rest of them are precipitated only by complete saturation with ammonium sulfate and are not precipitated by nitric or picric acids. Some of the proteoses are quite toxic, especially those from albumins. Peptones, which are further hydrolytic products, are not salted out by ammonium sulfate and are not precipitated with the usual reagents.

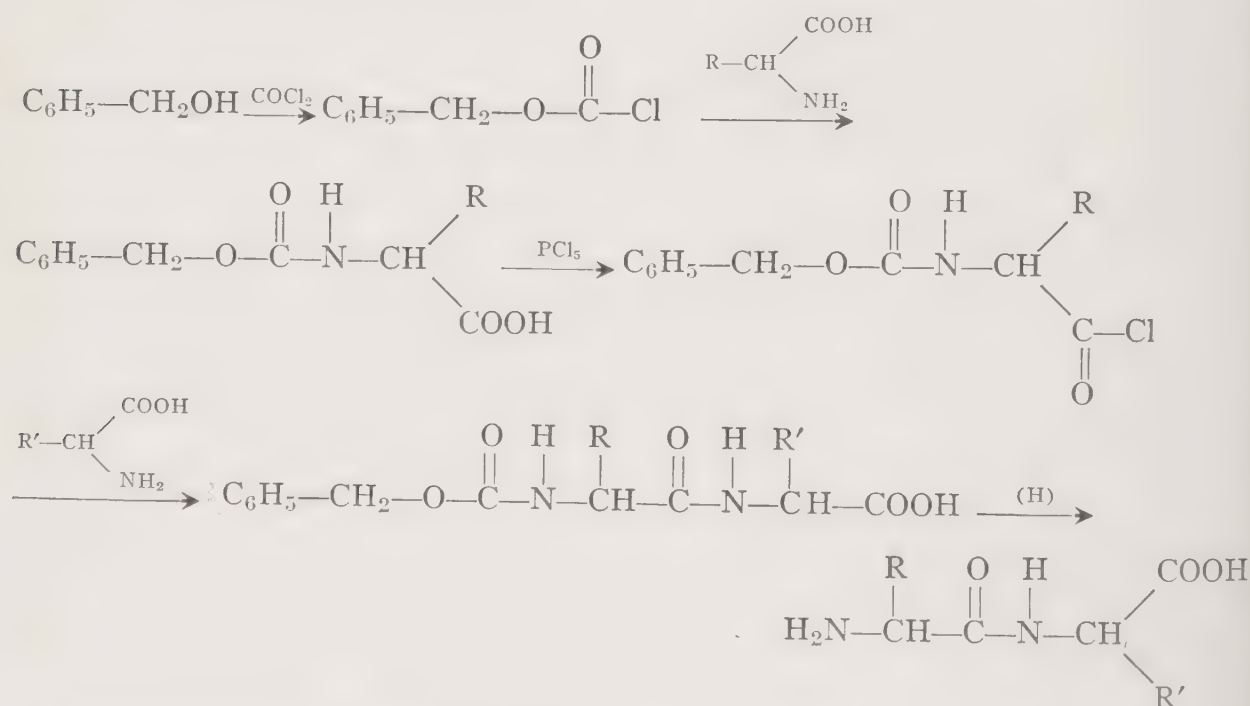
The peptides may possibly represent the last stage before amino acids in the hydrolytic process, but they are generally artificial. They have properties similar to those of the peptones, although the latter have a much higher molecular weight. Excepting the dipeptides, the preparation of these is not an easy task, as witness the fact that, since Fischer's pioneer work, 1901 through 1907, little progress has been made toward building up large molecules. A dipeptide may be formed by dehydrating the amino acid or a mixture and hydrolyzing the resulting diketopiperazine in an appropriate manner.



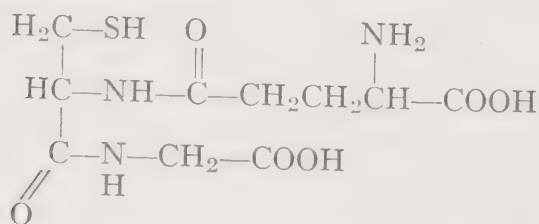
tissue. Lecithoproteins have not been studied extensively, but one of them is present in the yolk of eggs. Chromoproteins are also called hemoglobins since the best known

Since the dipeptide is still an amino acid, it should be possible to combine with a third molecule and continue the process indefinitely. Fischer was able to build up peptides composed of as many as 18 separate

units, by using esters in some cases and halogen derivatives in others, until the peptide linkage was formed. Since that time there have been devised other methods that give opportunities to put in the more interesting compounds, such as tyrosine and tryptophane. The best means to date is that, formulated by Bergmann, of protecting amino groups by the carbobenzoxy radical $\text{C}_6\text{H}_5\text{—CH}_2\text{—O—CO—}$. The necessary reagent, made by the reaction of phosgene and benzyl alcohol, is treated with the amino acid or peptide, when all free amino groups are masked. The resulting product can be converted to the acid chloride and then combined with other peptides through the carboxyl group. Finally, the carbobenzoxy radical can be eliminated by reduction.



A modification of this method was successful in 1935 in producing the important tripeptide glutathione from cysteine, glycine and glutamic acid.



Glutathione is very widely distributed in

animal and vegetable tissues; indeed, it is found in so many places that it must be assumed that it has an important role in metabolism, probably in oxidation-reduction reactions because of the sulfhydryl group. It is also suggested that it may be a source for its three constituents, which are known to function in detoxications.

Gelatin U.S.P. is a protein obtained by the partial hydrolysis of collagen, an albuminoid found in bones, skins, tendons, cartilage, hoofs and other animal tissues. The products seem to be of great variety, and, from a technical standpoint, the raw material must be selected according to the purpose intended. The reason for this is that collagen usually is accompanied in nature by

elastin and especially by mucoids, such as chondromucoid, which enter into the product in small amount. The raw materials for official gelatin, and also that used generally for a food, are skins of calf or swine and bones. The bones are first treated with hydrochloric acid to remove the calcium compounds and then digested with lime for a prolonged period, which converts most other impurities to a soluble form. The fairly pure collagen then is extracted with hot water at pH of

about 5.5, and the aqueous solution of gelatin is concentrated, filtered and cooled to a stiff gel. Calf skins are treated in about the same way, but those from hogs are not given any lime treatment. The product from bones or calf skins has an isoelectric point of 4.7 to 5.0, that from hog skins 7 to 9, as judged by the pH at maximum turbidity in a 2 per cent solution when cooled to 0° C. The minimum of gel strength officially is that a 1 per cent solution, kept at 0° C. for six hours, must show no perceptible flow when the container is inverted.

Gelatin occurs in sheets, shreds, flakes or coarse powder. It is white or yellowish, has a slight but characteristic odor and taste, and is stable in dry air but subject to microbial decomposition if moist or in solution. It is insoluble in cold water but swells and softens when immersed and gradually absorbs 5 to 10 times its own weight of water. It dissolves in hot water to form a colloidal solution; it also dissolves in acetic acid and in hot dilute glycerin. In 1 per cent solution, it gives precipitates with chromic acid and with picric acid and produces a turbidity with tannic acid at a dilution of 1:5,000. Gelatin is commonly bleached with sulfur dioxide, but that used medicinally must have not over 0.004 per cent of sulfur dioxide. However, a proviso is made that for the manufacture of capsules or pills it may have certified colors added, may contain as much as 0.15 per cent of sulfur dioxide and may have a lower gel strength.

Gelatin is used in the preparation of capsules and in the coating of pills and, with glycerin, as a vehicle for suppositories. It also has been employed as a vehicle for other drugs when slow absorption is required. When dissolved in water, the solution becomes somewhat viscous, and at one time such solutions were used to replace the loss in blood volume in cases of shock. This is more efficiently accomplished now with blood plasma, which is less dangerous. In hemorrhagic conditions, it sometimes is administered intravenously to increase the

clotting of blood or is applied locally for the treatment of wounds.

The most important value in therapy is as an easily digested and adjuvant food. It fails to provide any tryptophane at all and is notably lacking in adequate amounts of other essential acids; approximately 60 per cent of the total acids consists of glycine and the prolines. Nevertheless, it is very useful when supplemented in various forms of malnutrition, gastric hyperacidity or ulcer, convalescence and generally diets of the sick. It is specially recommended in the preparation of modified milk formulas for feeding infants.

OFFICIAL OCCURRENCE U.S.P.	PER CENT GELATIN
Glycerinated Gelatin	50.0

Absorbable Gelatin Sponge (Gelfoam)
N.N.R. is designed as a surgical sponge to be left in place after the closure of an operative wound, particularly when moistened thoroughly with an isotonic solution of thrombin.

Iodalbin is a product made by the action of iodine on serum albumin. It is a reddish powder that is soluble in alkalies but not in water. It has been used for therapy with iodine instead of inorganic salts, in doses of 0.3 to 0.6 gram, and is claimed to be as efficient and less disagreeable.

Bismutose (Bismuth Albuminate) is made with an albuminoid and contains about 22 per cent of bismuth. It is a pale gray or white powder that is only partly soluble in water and is intended to be used in doses of 0.5 to 1.0 gram for intestinal cramps.

Casein, the chief protein of milk, easily is obtained in fairly pure form by precipitating the fat-free serum with acid. It is a white or yellowish, granular powder that is insoluble in water but soluble in dilute mineral acids or alkalies. It is used extensively in industry for making plastics, casein glue, a wool-like fiber, cold-water paints and cosmetics. In the dispensary, it has some value in emulsions and creams, but its chief importance in medicine is for making protein

hydrolysates, because hydrolysis of the compound gives all of the essential amino acids in satisfactory amounts; such proteins are described as "adequate." Solutions of casein that are highly purified have been injected for nonspecific protein therapy. Iodocasein, a product made in the same way as other iodoproteins, has been used in place of inorganic iodides. A calcium salt (Casec) is recommended as an accessory food for high protein diets and to be used for infants in summer diarrhea. The sodium salt (Casein-Sodium) also has been recommended as an adjunct food.

Gastric Mucin N.N.R. is prepared by digesting the lining of hog's stomachs with pepsin and precipitation from the supernatant liquid with 60 per cent alcohol. It is a white to yellow powder or brownish-yellow granules and forms a viscous, gray, opalescent solution with water. It probably contains proteoses and peptones derived from the glycoprotein mucin. It is employed in a dose of 2.5 grams every two hours in the treatment of gastric ulcer and hyperchlorhydria, where it acts as an emollient and neutralizes acid.

Beef Extract N.F. is the residue from beef broth obtained by extracting fresh, sound, lean beef by cooking with water and evaporating the broth at low temperature, usually in a vacuum, until a thick, pasty residue is obtained. It consists of a yellowish-brown to dark brown, slightly acid, pasty mass, having an agreeable, meatlike odor and taste. It is soluble in 10 times its weight of water to yield a nearly clear solution, free from sediment. At least 90 per cent of the solids are soluble in dilute alcohol, and these alcohol-soluble solids must contain at least 6 per cent of nitrogen. The total solids, comprising about 75 per cent of the extract, must contain not more than 0.35 per cent of amide ammonia.

Beef extract, as well as similar extracts in commerce, contains natural salts, meat bases such as xanthine and noncoagulable protein, including gelatin and proteoses. In the small

doses of these used, the amount of nutrient is insignificant, but the meaty flavor and odor are excellent stomachics. The alcoholic solution of beef, iron and wine presents, in addition, therapeutic doses of ferric ammonium citrate.

OFFICIAL OCCURRENCE	PER CENT BEEF EXTRACT
N.F.	
Beef, Iron and Wine.....	3.0

Peptonized Iron (Iron Peptonate) N.F. is a compound of iron oxide and peptone which is rendered soluble by the addition of sodium citrate "and yields not less than 16 per cent and not more than 18 per cent of Fe." It occurs as dark brown, lustrous granules, or as a brown powder, having a characteristic odor and taste, and is affected by light. It is freely soluble in water, but is insoluble in alcohol; the aqueous solution is neutral or alkaline to litmus paper. It is used in 0.3 gram doses for iron therapy and, although it is free from astringency or tendency to irritate the gastro-intestinal membranes, is probably of no advantage over other iron preparations. The amounts of iron (0.3 per cent) and manganese (0.13 per cent) in the manganese combination are too small to be of any appreciable value in the official dose of 8 cc.

OFFICIAL OCCURRENCE	PER CENT PEPTONIZED IRON
N.F.	
Peptonized Iron and Manganese Solution	1.75

ENZYMES

Included among the proteins are the important substances that are known as enzymes or biocatalysts. These are the organic catalytic agents that are so necessary for most of the metabolic processes in both plants and animals. The names are coined by adding -ase to a root indicating the substance or group of substances on which the catalyzed reaction takes place, for example, histaminase, proteinase, sucrase and lipase. Several of the enzymes known before this modern convention was adopted are still

called by older names, for example, pepsin, trypsin and rennin. The material upon which they act is called the substrate, and this is obviously indicated in the name. They are soluble in water, in dilute alcohol and in dilute glycerin, and they are precipitated from aqueous solutions by neutral salts and by the majority of protein precipitants. In addition to these properties, they migrate during the passage of an electric current except when the pH is at the isoelectric point. A few of the hundreds of enzymes known have been obtained in the crystalline state during the past few years (see Table 57).

period, is able to inhibit their power and sometimes destroy them. Loss of activity likewise is brought about by various reagents, such as strong acids and bases, formaldehyde, oxidizing agents and salts of heavy metals. On the other hand, a few substances that often kill living organisms such as yeast have little effect on the enzymes and can be used to preserve them; chloroform and thymol commonly are used for this purpose. Any inactivation is almost always permanent, but removal of the detrimental material, if mild or after a short contact, may sometimes restore the power.

TABLE 57. ENZYMES OBTAINED IN THE CRYSTALLINE STATE, 1926-1946

ENZYME	WHEN	PREPARATION BY WHOM
Urease	1926	Sumner
Pepsin	1930	Northrup
Amylase	1931	Caldwell, Bocher and Sherman
Trypsin	1932	Northrup and Kunitz
Chymotrypsin	1933	" " "
Yellow Oxidase	1934	Theorell
Ficin	1937	Walti
Carboxypeptidase	1937	Anson
Lysozyme	1937	Abraham and Robinson
Catalase	1937	Sumner and Dounce
Papain	1937	Bells and Lineweaver
Ribonuclease	1939	Kunitz
Tyrosinase	1939	Dalton and Nelson
Ascorbic Acid Oxidase	1939	Tadokoro and Takasugi
Lactic Dehydrogenase	1940	Straub
Fumarase	1940	Laki and Laki
Phosphorylase	1942	Green and Cori
Transphosphorylase		
Phosphopyruvate	1944	Kubowitz
Phosphomonoesterase	1944	Van Thoai, Roche and Sartori
Mexicain	1945	Castaneda-Agullo <i>et al.</i>
Rennin	1945	Berridge
Phosphorylase-b	1945	Cori and Cori
Glyceraldehyde		
Dehydrogenase	1945	Cori, Slein and Cori
Hexokinase	1946	Kunitz and McDonald

The enzymes are easily inactivated or destroyed by certain conditions or reagents, a denaturing process as with other proteins. Most of them lose their activity when their solutions are heated for a short time above 80 to 90° C., although in the dry state they may not be affected by this temperature for a reasonable length of time. Ultraviolet light, or even ordinary sunlight for a sufficient

The enzymes conform strictly to the usual definition of a catalytic agent, but in some ways they are unique. The speed of the reaction is altered, either decreased or increased, in proportion to the amount of enzyme present. Theoretically, a minimum amount can affect any quantity of the substrate, providing there is enough time, but practically, some is always destroyed at the

same time and often the accumulation of products tends to inhibit the activity. The enzyme itself does not appear to take part in the reaction, although it would seem reasonable to presume that it must be changed and this change reversed many times while the reaction is proceeding. Sometimes it will promote the reverse reaction, such as building up carbohydrates when the usual effect is to hydrolyze the same compound. The enzymes differ from other catalysts in that their power is entirely specific, though it may be limited to common groups of substances, rather than to a single compound. They also differ in being able to induce reactions, a condition that is probably essential in the living organisms, where changes of temperature and other tools of the chemist are lacking. Their action is greatly influenced by small changes in temperature or pH and possibly also by dilution, and for each enzyme there is a maximum and minimum value above and below which activity is nil. Generally, the pH range is from 2 to 8 and the temperature range from 20° to 55° C. Often they exist in the organism in a masked or inactive state (zymogen or proenzyme), being combined with some other compound that must be removed before there will be any activity. Thus, pepsin circulates as pepsinogen and does not have any effect upon proteins until it is set free by acids.

Some enzymes consist of a protein combined with another substance called the coenzyme, although it is not an enzyme at all but merely a necessary part. In other words, the protein alone has no activity (it has been termed an apoenzyme), nor has the coenzyme in the absence of the apoenzyme. The union may be firm as in conjugated proteins, but it is sometimes loose enough to be severable by such a simple operation as dialysis. A number of enzymes contain small amounts of metals, such as iron, copper, manganese, magnesium, zinc or vanadium, and in a few cases the activity has been shown to be dependent upon the presence of this metal. Further, certain amylases, if not many other en-

zymes, seem to give best results in the presence of a particular electrolyte, or rather a particular ion, usually the anion. In nature there sometimes appears to be present an inhibiting substance or antienzyme which is protein in character, and some investigators have suggested that all metabolic processes are controlled by the activities of enzyme and inhibitor. However, some prefer to limit the term antienzyme to such substances as antibodies that arise through an immunization reaction.

In the assay of enzymes, in addition to the amounts used and the necessity of adhering strictly to a given set of conditions, it must be emphasized that time is a very important factor. To say that pepsin will digest not less than 3,000 times its own weight of egg albumin means nothing at all. Theoretically, any amount of active pepsin will do this if enough time is allowed; hence, any purity rubric should state the amount of time definitely.

The enzymes are classified according to the nature of the substrate and of the reaction. Most of them are hydrolytic (hydro-lases), some are of the oxidation-reduction type, and a few bring about miscellaneous reactions. Table 58 (page 567) shows some of the important enzymes, with the substrate of each and the chief end-product.

Pancreatin U.S.P. is a substance obtained from the fresh pancreas of the hog or of the ox and contains a mixture of enzymes, principally pancreatic amylase (amylase), trypsin and pancreatic lipase (steapsin). It "converts not less than 25 times its weight of U.S.P. Potato Starch Reference Standard into soluble carbohydrates, and not less than 25 times its weight of casein into proteoses. Pancreatin of a higher digestive power may be brought to this standard by admixture with lactose, or with sucrose containing not more than 3.25 per cent of starch, or with pancreatin of lower digestive power." The time allowed in the assay, which is fundamentally important and should have been

TABLE 58. ENZYMES, THEIR SUBSTRATES AND CHIEF END-PRODUCTS

HYDROLASES			
TYPE	ENZYME	SUBSTRATE	CHIEF END-PRODUCT
ESTERASES	Pancreatic Lipase (Steapsin)	Fats	Mono and Diglycerides
	Cholinesterase	Acetylcholine	Choline
	Phosphatase	Nucleotides	Nucleosides
CARBOHYDRASES	Pancreatic Amylase (amyllopsin)	Carbohydrates	Monosaccharides
	Salivary Amylase (Ptyalin)	Carbohydrates	Monosaccharides
	Malt Diastase	Carbohydrates	Maltose
	Sucrase (Invertase)	Sucrose	Dextrose, Levulose
	Lactase	Lactose	Dextrose, Galactose
	Maltase	Maltose	Dextrose
PROTEASES	Pepsin	Protein	Proteose, Peptone
	Trypsin	Protein	Peptides
	Papain	Protein	Peptides
	Carboxypeptidase	Carboxypeptides	Amino Acids
	Rennin	Casein	Paracasein
AMIDASES	Urease	Urea	Ammonia
	Arginase	Arginine	Urea, Ornithine
OXIDIZING-REDUCING			
	Oxidoreductase (Zymase)	Hexoses	Alcohol
	Carboxylase	Keto-Acids	Aldehyde
	Catalase	Hydrogen Peroxide	Oxygen

included in the rubric, is five minutes for starch and one hour for casein. Pancreatin is a cream-colored, amorphous powder having a faint, characteristic, but not offensive odor. It is slowly but incompletely soluble in water and insoluble in alcohol. It acts best in neutral or faintly alkaline media, and excessive acid or alkali renders it inert. Pancreatin can be prepared by extracting the fresh gland with 25 per cent alcohol, or with water, and subsequently precipitating with alcohol. Besides the enzymes mentioned, it contains some trypsinogen, which can be activated by enterokinase of the intestines, chymotrypsinogen, which is converted by trypsin to chymotrypsin, and carboxypeptidase.

Pancreatin is used largely for the predigestion of food and for the preparation of hydrolysates. It originally was introduced as an emulsifying agent but, with the advent of more effective substances for this purpose, is not now much used in this way. The value of its enzymes orally must be very small because they are digested by pepsin and acid in the stomach, although some of them may escape into the intestines without

change. Even if they are protected by enteric coatings, it is doubtful if they could be of great assistance in digestion. Pancreatin has been recommended in the official dose of 0.5 gram in gastric and intestinal achylia, but is probably of little value. It has also been applied topically for removing the false membrane of diphtheria and dead tissue in cancers and for the treatment of tuberculous abscesses.

Malt Extract N.F. is obtained by extracting malt, the partially and artificially germinated grain of one or more varieties of barley, *Hordeum vulgare* L. The malt is infused with water at 60° C., and the expressed liquid is concentrated under reduced pressure at not over 60°, and may be mixed with 10 per cent of glycerin. It is a sweet, viscous, light brown liquid with an agreeable, characteristic odor and is soluble in warm water. The aqueous solution is not clear and deposits a voluminous, flocculent precipitate on standing. The extract "is capable of converting not less than 5 per cent of starch into water-soluble sugars" in 30 minutes. It contains dextrin, maltose, a small amount of glucose, a proteolytic enzyme and partic-

ularly diastase, which converts starch into maltose at an optimum temperature of 55° C. By some manufacturers, its strength is expressed in Lintner degrees after an assay on 2 per cent starch solution at 70° C. and a pH of 4.6.

Malt extract is employed to some extent in medicine in a dose of 15 grams as an easily assimilable food; formerly, it was used as an aid in digestion in certain types of dyspepsia, where it can be of small value. The most important use today, however, is as a vehicle for cod-liver oil and other therapeutic agents.

Takadiastase is derived from the action of a fungus, *Aspergillus Oryzae* Cohn (*Eurotium O. Ahlburg*), on rice hulls or wheat bran. It is a yellowish, hygroscopic, almost tasteless powder that is freely soluble in water and can solubilize 300 times its weight of starch in 10 minutes. It is employed in doses of 0.3 to 1.0 gram in the same conditions as malt diastase.

Pepsin N.F. is a substance containing a proteolytic enzyme obtained from the glandular layer of the fresh stomach of the hog. When assayed as directed, it "digests not less than 3000 and not more than 3500 times its weight of egg albumin" in 30 minutes. A pepsin of higher digestive power may be reduced to the official standard by admixture with a pepsin of lower power or with lactose. The official material occurs as lustrous, transparent or translucent scales; as a granular or spongy mass, ranging in color from weak yellow to light brown; or as a fine, white to weakly yellow, amorphous powder. It is free from offensive odor, has a slightly acid or salty taste and is not more than slightly hygroscopic, although it dissolves freely in water to give an opalescent solution. Dry pepsin is not injured by heating to 100° C.; in solution, it is rapidly destroyed by alkalies, by temperatures in excess of 70° C., and by other proteolytic enzymes.

The enzyme itself can be obtained from materials such as the official article by dialysis against dilute acid in concentrated

solution. By the aid of low temperatures, it has been crystallized in six-sided pyramids that are soluble in strong acids or alkalies but are insoluble at a pH of 3. Its activity in the official assay is about 1:20,000.

Pepsin has been used locally to remove dead tissue in cancer, sloughing ulcers, the false membrane of diphtheria or in wounds. Internally it can be employed where there is a deficiency of the natural enzyme, but it is not entirely necessary to proteolytic digestion because the intestinal and pancreatic enzymes can function entirely unaided by pepsin, and administration of the latter can accomplish very little. Furthermore, many of the preparations are devoid of activity because this is so easily destroyed by admixture with reagents and by various other conditions. A more logical use of pepsin is in preparation of predigested foods, when it must be added alone in an active form with a trace of acid. The dose is given officially as 0.5 gram.

Enzymol, formerly described as an extract of fresh animal stomach, was designed for local application.

OFFICIAL OCCURENCE N.F.	PER CENT PEPSIN
Pepsin Elixir	3.5
Compound Pepsin Elixir	3.5
Saccharated Pepsin	10.0
Pepsin and Rennin Elixir	4.5

Papain N.F. (Papayotin, Papoid, Caroid), the dried and purified latex of the fruit of *Carica Papaya* L. (Fam. *Caricaceae*), has the power of digesting protein in either acid or alkaline media, best at a pH of from 4 to 7, and at 65 to 90° C. The activity is greatly increased by the presence of glutathione, hydrogen sulfide or cyanides. It occurs as light brownish-gray to weakly reddish-brown granules or as a yellowish-gray to weakly yellow powder. It has a characteristic odor and taste and is incompletely soluble in water to form an opalescent solution. The commercial material is prepared by evaporating the juice, but the pure enzyme also has been prepared and crystallized.

The chief use of papain is to tenderize beef commercially, in which case the crude substance is smeared on or mixed intimately before cooking; about 250,000 pounds are used annually in this way in the United States. It is also employed in the brewing industry to make "chill-proof" beer, where it removes the proteins that would precipitate on cooling, and in the tanning industry to prepare hides. In medicine it has been used locally in various conditions similar to those for which pepsin is employed. It has the advantage of activity over a wider range of conditions, but it is often much less reliable. Intraperitoneal instillation of a weak solution has been recommended to counteract a tendency to adhesions after abdominal operations, and several enthusiastic reports have been made about the value under these conditions. Papain has been reported to cause allergies in persons who handle it, especially those who are exposed to inhalation of the powder.

Bromelin is a somewhat similar proteolytic enzyme from the pineapple, *Ananas comosus* (L.) Merr., and can be prepared from the juice by precipitating with ammonium sulfate or by alcohol. Its activity is greatest at a pH of from 3 to 4. It has been suggested as an anthelmintic because it has the power of digesting living worms in a test tube.

Rennin N.F. (Rennet, Chymosin, Seriparium) is the partially purified milk-curdling enzyme obtained from the glandular layer of the fourth stomach of the calf. It "possesses a coagulating activity of not less than 90 per cent and not more than 110 per cent of the Reference Rennin . . . Rennin of a higher coagulating power may be brought to the requisite strength by admixture with lactose or sodium chloride or both." The assay is made on milk at a temperature of 43° C., and the criterion for the end-point is the time required to thicken the milk, as shown by a distinctly convex surface when the vessel is tipped to an angle of about 45°. Rennin occurs as a yellowish-

white, hygroscopic powder, or as yellow grains or scales, having a characteristic and slightly salty taste and a peculiar, not unpleasant, odor. It is partly soluble in water and in diluted alcohol. Rennin is sold as junket tablets for the preparation of thickened foods from milk, and large quantities are employed in the cheese industry. Occasionally, it is administered to assist in the digestion of casein, especially in infants.

INSULIN

Insulin Injection (Insulin, Insulin Hydrochloride) U.S.P. (Iletin) "is an acidified solution of the active principle of the pancreas which affects the metabolism of glucose." It is a clear, colorless or almost colorless liquid and must contain: 0.1 to 0.25 per cent (W/V) of phenol or cresol, 1.4 to 1.8 per cent (W/V) of glycerin, not more than 0.4 milligram (0.16 to 0.4 milligrams if made from the crystals) of zinc per 1,000 units, not over 0.85 milligrams (0.65 milligrams if made from the crystals) of nitrogen per 100 units and must have a pH of from 2.5 to 3.5. It is supplied in such concentration that each cubic centimeter contains 20, 40, 80 or 100 units, as measured against a standard solution of reference zinc-insulin crystals in rabbits.

Insulin is a protein that is produced by the islands of Langerhans in the pancreas and is intimately concerned with carbohydrate metabolism. Since 1889 it has been known that the pancreas contains something that regulates glucogenesis and whose absence leads to a pathologic condition similar to, if not identical with, diabetes mellitus. It was not until 1921, however, that Banting, Best and Macleod proved its existence, devised a method of preparation in solution and pointed the way to making it in pure form. The preparation was accomplished by Abel and colleagues in 1926. The modern method of preparation depends upon the facts that it is soluble in dilute alcohol up to 80 per cent at a pH of from 3 to 3.5 but not in absolute alcohol, that it can be salted out by am-

monium sulfate and is insoluble in acetone or pyridine, and that it can be precipitated at its isoelectric point (5.35) or by picric acid.

The composition of pure insulin is fairly clear, although accumulation of the necessary data has come from various laboratories and over many years. The molecular weight is about 38,000, and the relative amounts of amino acid obtained from it are as follows: leucine and isoleucine, 30.0 per cent; glutamic acid, 30.0; tyrosine, 12.2; cystine and cysteine, 12.2; histidine, 8.0; arginine, 3.2; lysine, 2.3; serine, 3.6; threonine, 3.6; prolines, phenylalanine and methionine in small amounts; glycine, alanine, valine, norleucine, tryptophane, aspartic acid and hydroxyglutamic acid are absent. The total, taking into account the water added for hydrolysis, is about 100 per cent. The amount of sulfur is about what would be given by the cystine, so that the quantity of methionine must be very small. Insulin also contains an amount of zinc that is variable (0.3-0.6 per cent), suggesting that some of it may be in the form of inorganic salts, but it is indicated that there are about 3 atoms per molecule.

Assay of the official product is based on a comparison with a reference standard of crystalline zinc-insulin, which is by international agreement defined as having 22 units per milligram. Suitable dilutions of both are injected into groups of rabbits, and the amount of reduction of blood sugar after 1.5, 3 and between 4 and 5.5 hours is determined for each. The determination of blood sugar is made by precipitating the blood with zinc hydroxide, adding alkaline cupric iodide and finally titrating the acidified solution for excess iodine.

There are specific regulations in regard to labeling the finished packages. Each must contain on the outside wrapper information on the batch mark, strength in terms of units per cc., expiration date (two years) and the warning "Keep in a cool place; Avoid freezing." Furthermore, the outside con-

tainer or wrapper must be distinguished by colors according to number of units per cc.: yellow for 20, red for 40, green for 80 and orange for 100. If the material was made from insulin in the crystalline form, the colors are: blue and gray or blue, gray and yellow for 20; red and gray for 40 and green and gray for 80 units.

Insulin is manufactured in the pancreas and has an effect on the metabolism of carbohydrates and lipids. The principal result of administration is to reduce the level of sugar in the blood when this is high, as is the case in diabetes; in fact, the discovery of this function of the gland was made when it was found that removal of the pancreas produced symptoms very similar to those of diabetes. The role of insulin apparently is connected with the essential metabolic process, the phosphorylation of glucose. The phosphate ester of glucose (glucose-6-phosphate) is formed as the result of the action of the enzyme hexokinase. This enzymatic action is blocked in the presence of a hormone from the anterior pituitary gland, thus preventing glycogenesis and glycolysis. Insulin absolves the hexokinase activity, demonstrating an antagonistic action between it and the anterior pituitary hormone. Excessive doses or hypersecretion lead to weakness, fatigue, disorientation, profuse sweating, unconsciousness and irregular convulsions. Unless the condition is treated by oral administration of glucose, or intravenously if the patient is comatose, death may result; the mortality in animals is about 40 per cent.

Insulin is almost a specific in the control of diabetic symptoms, although its lack is probably not the sole cause of the disease. If the case is light, there may be gradual recovery by the diseased pancreas, and the patient may be able to live normally by regulation of diet alone. In the more severe cases, however, the administration must be continued indefinitely because insulin does not cure but is for replacement therapy only. The dosage to be used needs careful super-

vision because of the various factors involved and because the need alters from time to time. The chief conditions that must be considered are self ability to produce insulin, level of sugar in the blood and intake of food. In making any calculations it is considered that a unit will take care of about 1.5 grams of dextrose in the diet, and the production by the patient can be measured by his ability to utilize extra carbohydrate without extra insulin. The treatment can also be employed to get diabetic patients in shape for operation and to relieve those who are suffering from complicating infections. Cases of resistance to insulin and hypersensitivity have been encountered; the latter can be overcome by a desensitizing program. However, in some of these the susceptibility may largely be due to other components of commercial insulin, and the untoward reactions may be eliminated by using a solution of the crystalline zinc-insulin.

The preparations are almost always administered by subcutaneous injection. They cannot be given orally because, although many devices have been employed to overcome it, insulin is either digested by the proteolytic enzymes of the gastro-intestinal tract or is very little absorbed. It can be given intravenously but is nowhere nearly as effective by that route because it is too rapidly excreted by the kidneys. Even when it is used subcutaneously, the action is very short, and the injection must be repeated two or three times a day. In order to obviate this need, there have been developed the combinations with protamine and with globin, from which the maximum reducing power is reached in a longer time but is sustained, so that injections are needed less frequently.

Protamine Zinc-Insulin Injection U.S.P. is a suspension in a buffered aqueous medium of insulin modified by zinc chloride and protamine. The latter is prepared from the sperm or from the mature testes of fish belonging to the genera *Oncorhynchus* Suckley, *Salmo* L., or *Trutta* Jordan and Evermann (Family *Salmonidae*). It must contain: 1.4

to 1.8 per cent (W/V) of glycerin, 0.18 to 0.22 per cent of cresol or 0.22 to 0.28 per cent (W/V) of phenol, 0.15 to 0.25 per cent (W/V) of sodium phosphate, 0.20 to 0.25 milligram of zinc and 1.0 to 1.5 milligrams of protamine per 100 units, and not over 1.25 milligrams of nitrogen per 100 units. For standardization, the samples of blood are taken every 1.5 to 3.0 hours over not less than 11 hours. It must be brought into uniform suspension by carefully shaking before use. The packages are distinguished by colors of red and white for 40 units per cc. and green and white for 80 units.

The clinical administration is the same as for the unmodified preparation, but the effects reach a maximum in about 12 to 24 hours, and an injection is not usually needed oftener than once a day. Its employment can be accompanied by treatment with the ordinary product. In those cases where hyperinsulinism occurs, the symptoms may be prolonged in such a way that treatment with carbohydrates must be carried on even after apparent recovery.

Globin Insulin with Zinc N.N.R. is a sterile preparation in a hydrochloric acid medium of insulin modified by the addition of zinc chloride and globin derived from hemoglobin of beef blood. According to regulations of the Federal Security Agency, the product contains per 100 units: 3.6 to 4.0 milligrams of globin, calculated as 6 times its nitrogen content; 0.25 to 0.35 milligram of zinc and not more than 1.5 milligrams of total nitrogen. It also contains 1.3 to 1.7 per cent (W/V) of glycerin and 0.15 to 0.20 per cent (W/V) of cresol or 0.20 to 0.26 per cent (W/V) of phenol, and has a pH of from 3.4 to 3.8.

The duration of effect is intermediate between that of regular insulin and protamine zinc-insulin; the period of greatest action is 8 to 16 hours after injection. Otherwise, the indications for its use and dosage are, in general, similar to those for the protamine combination.

Zinc Insulin Crystals N.N.R. consists of small, colorless crystals that are sparingly soluble in water but are soluble in dilute acid or alkali, the isoelectric point being about 5.3. They are stable if kept at low temperature. The zinc content is 0.45 to 0.9 per cent, and each milligram is equivalent to not less than 22 units.

Crystalline Zinc Insulin Injection N.N.R. is a solution of the crystals that meets the requirements for identity and purity of the U.S.P Insulin Injection. It usually is reserved for the treatment of patients who have exhibited allergic reactions to the regular insulin.

BLOOD PRODUCTS

The blood as the circulating medium of the body, has numerous functions but is not believed to be the site of any metabolic processes. It distributes nutriment, transfers oxygen and carbon dioxide between the lungs and the tissues, collects and delivers waste materials, acts as a buffer to acids and alkalis, regulates isotonicity by adding or subtracting water and distributes many agents that are needed at different points, for example, immune bodies, other protective agents, hormones and enzymes of various types. Its composition, therefore, will change markedly during altering conditions, although it is fairly constant under normal circumstances. About 45 per cent consists of corpuscles that can be separated by centrifuging, and of these, only about 0.2 per cent are other than erythrocytes. The 55 per cent of removed plasma contains about 7 to 8.7 per cent of solids, of which a small portion (less than 1 per cent) can be removed by clotting to produce the defibrinated plasma, which is called the serum.

The serum contains some inorganic salts and simple organic compounds, but the total solids are chiefly protein, mostly albumin and the rest nearly all globulin. The inorganic anions are mainly chloride, sulfate and phosphate, and the cations are magnesium, calcium, sodium, potassium, copper and iron.

Some of the simple organic compounds are urea, uric acid, creatine, creatinine, dextrose, cholesterol, fatty acids, lecithin, bile pigments, carbonates, ascorbic acid and other vitamins, hormones, phenols and lactic acid. In the serum also are many of the substances that are associated with development of immunity, such as opsonins and antitoxins. In addition, the plasma contains the protein fibrinogen, which is converted by coagulation to insoluble fibrin, and the separated serum has an excess of the clotting agent thrombin.

The serum globulins can be obtained by salting out with magnesium sulfate or half saturation with ammonium sulfate. They can be subdivided by various solubility methods into euglobulin and pseudoglobulin, but more particularly by electrophoresis into alpha, beta and gamma globulins that contain most of the antibodies. The serum albumins, which are in about double the amount of globulins, can be isolated by completely saturating the filtrate with ammonium sulfate and can probably be separated into several individual albumins. It has been found that regeneration of all of these proteins in the serum is best accomplished by feeding whole blood or liver.

The clotting process is a very important one to prevent excessive bleeding in cases of operation or wounding. The time required for this is normally about 5 minutes, and any prolongation beyond 10 minutes is considered to be abnormal and require treatment. Thrombin, the agent or enzyme that is partly responsible for bringing about the clotting process, is contained in the blood in the inactive form, prothrombin, and calcium salts seem to be necessary to set it free in the active state. However, this cannot occur in the blood because the prothrombin is present combined with an inhibiting agent that is called antiprothrombin. Antiprothrombin can only be removed by the action of a substance that is usually termed thromboplastin or thrombokinase. This apparently is contained in the thrombocytes, and also

probably is present in many tissues that are not directly accessible to the blood. When blood is shed, the thrombocytes disintegrate to liberate thromboplastin, this releases prothrombin, and calcium salts finally activate the prothrombin to thrombin. The last then converts fibrinogen to fibrin to complete the process. Fibrinogen, which can be prepared in a relatively pure state, resembles globulins in that it is insoluble in water but dissolves in dilute salt solution and can again be precipitated by increasing the amount of salt. The change during the formation of fibrin is not understood and could be a denaturation. The anti-prothrombin is assumed to be identical with heparin, a compound obtained from connective tissue and particularly in the walls of the liver. It has no effect on the activity of thrombin, but antithrombins are known to exist, such as hirudin of leeches. Little is known about the composition of thromboplastin, which can be obtained from disintegrating tissue cells of various types, but it is probable that several substances can assume the role of releasing prothrombin.

Thrombin can be prepared by extraction of clotted blood with 8 per cent sodium chloride after soluble proteins have been removed by water. It also can be obtained by precipitating serum with alcohol and extracting the dried product with water; if plasma is employed in place of serum, the product is unable to clot blood until activated by calcium ions, due to the fact that it contains only prothrombin.

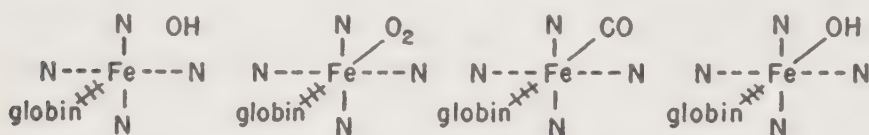
The human erythrocytes are specialized cells in the form of biconcave discs, although they may occasionally assume a cup-shape, and are 7.5 to 9.5 microns in diameter. The number per cubic millimeter averages about 5,000,000, but this is quite variable with sex (men have more than women), with age, with individuals, with conditions of living and particularly in the presence of disease. The production of these cells (hemopoiesis) in adults is carried out in special cells in the bone marrow, but in embryos it also

is carried out in the liver and spleen and, under pathologic conditions, probably in the lymph nodes. Furthermore, other organs are probably concerned in the production, although the mechanism is not known. The erythrocytes are being destroyed at all times by the Kupffer cells of the liver, probably for the function of supplying bile pigments and other substances, and also by other agencies, such as the reticulo-endothelial cells of the circulation. It has been estimated that the average life of an erythrocyte is 8 to 120 days.

The erythrocytes contain 32 to 35 per cent hemoglobin, about 60 per cent water and the rest as stroma. The last can be obtained, after hemolysis of the corpuscles by dilution, through the process of centrifuging and is found to consist of lecithin, cholesterol, inorganic salts and a protein, stromatin. Hemolysis of the corpuscles, or laking as it sometimes is called, may be brought about by hypotonic solution, by fat solvents, by bile salts which dissolve the lecithin, by soaps or alkalies, by saponins, by immune hemolysins and by hemolytic serums such as those from snake venom and numerous bacterial products. Determination of the concentration of hemoglobin in the blood is an important diagnostic procedure. The normal amount is 14 to 16 per cent and usually is taken as 15.6 for purposes of calculating the percentage of normal in the color index, the volume index or the saturation index.

Hemoglobin is a conjugated protein that consists of the histone, globin, combined with heme (hematin), which has already been described in Chapter 19 and has the formula $C_{34}H_{32}N_4O_4FeOH$. The latter can be isolated by action of hydrochloric acid to give hemin chloride, $C_{34}H_{32}N_4O_4Fe+Cl^-$. It is not known just how the globin is attached, but most evidence indicates that it is combined with the ferrous iron through one of the potential, secondary valences, just as is oxygen that is carried by the blood in the form of oxyhemoglobin. Certain oxidizing agents react to form methemoglobin, which is in-

capable of acting as an oxygen carrier because the iron is in the ferric state, while carbon monoxide will also add to prevent the addition of oxygen. Diagrammatically, these compounds can be represented as follows:



Crystalline hemoglobin has a minimal molecular weight of about 17,000, and its formula varies with the source, but typically about $(C_{740}H_{1200}N_{203}O_{200}S_2Fe)_n$, with n having a probable value of four. Globin has an isoelectric point of about 7.5 and furnishes amounts of the several amino acids that make it similar to albumins, except that histidine and leucine are high and glutamic acid is low. The amount of cystine varies with the species of animal but is usually less than one per cent.

The other corpuscles of the blood consist of leucocytes and thrombocytes (platelets). The latter are important for carrying the thromboplastin and to the pathologist for diagnostic purposes. The leucocytes or white corpuscles are classified by the cytologist into numerous subdivisions, but the most important types are granulocytes or true leucocytes (65 per cent) and the lymphocytes (30 per cent). They are nucleated and have ameboid motion, and the general composition is quite varied, including albumins, globulins, nucleoproteins, glycogen, phospholipids and cholesterol. They are mobilized during infection to counteract the bacteria, which they engulf and destroy (phagocytosis). The mobilization is enhanced by a substance called leucotaxin, which is liberated from injured tissue, and the phagocytosis is aided by opsonins, which prepare the bacteria for destruction. The final result of the action is production of a pus containing bacterial and tissue debris, as well as leucocytes, but the mechanism of action is unknown.

The defense armamentarium of the body also includes the formation of antibodies that act against antigens, such as bacteria, molds, protozoa, toxins and other foreign proteins, or possibly carbohydrates. All of

these antibodies are apparently proteins that are usually concentrated in the globulin fraction of the serum, and it has been suggested that they are globulins modified in structure in some way as to fit only the special needs. They include agglutinins, which cause clumping of the antigen cells or molecules, hemolysins and other cytolytins, which bring about destruction of cells, precipitins, which form precipitates with antigens, and antitoxins, which specifically counteract toxic products from organisms. These terms are rather loosely used and are probably more or less overlapping; e.g., an antitoxin may be active by precipitation. In order for any of them to act on the antigen, there is necessary a substance that is known as the complement or alexin, which is omnipresent and entirely nonspecific and apparently is a lipoprotein. The fixation of antigen-complement-antibody is an irreversible process. It is used in the Wassermann test to detect syphilitic organisms.

The practical aspects of the facts about antibody formation are utilized in the production of serums and vaccines for counteracting infections. To make an antitoxic serum, an animal is treated with the toxin until enough antibodies have been formed, and the serum from this animal is then used in man or other animals as immune serum for a specific disease, such as botulism, diphtheria, tetanus and scarlet fever. Antibacterial serums, made in the same way using bacteria as the antigen, include those for anthrax, undulant fever, erysipelas, influenza

and whooping cough. Vaccines are preparations of the antigen itself, diluted in such a way as to give a mild infection, so that when injected they serve to stimulate the formation of antibodies and thus produce an active immunity. Finally, the serum from humans, who have recovered from diseases, such as scarlet fever or measles, may be used in other persons to create an immunity, and for some diseases which are very widely spread, such as measles, pooled human serum may contain enough antibodies to treat the infection in others.

According to agglutination tests, human blood may be classified into four groups which are mutually incompatible, although the first of these sometimes has been called the universal type. Unfortunately, they have been given different names and one must know which system is being employed. The international system, probably most often used, is here noted, with those of Jansky and of Moss, respectively, in parentheses. The types and approximate percentage of incidence are: O(I,IV) 43, A(II,II) 42, B(III, III) 10, AB(IV,I) 5.

Discovery of the Rh factor in the blood was extremely significant. This is an agglutinin which was given the name because the original work was done on rhesus monkeys. About 86 per cent of human beings have this factor in the erythrocytes and are said to be Rh-positive, although more recent work has shown that there are at least five or six subtypes. The Rh-negative person will develop reactions if he receives a transfusion of Rh-positive blood; also, those persons who are positive may show a sensitivity if one of the subtype factors is missing. Besides the necessity of determining if the patient is Rh-negative before transfusion, this factor is important in marriage, because union of a positive father and a negative mother is apt to result in miscarriages, still-births or incidences of fatal erythroblastosis fetalis in the child.

Whole Blood was formerly used extensively for a variety of purposes but mostly to

give replacements in case of disease or loss. The method was frequently followed by severe reactions and even fatalities until 1901, when it was found that blood from humans could be divided into four types on the basis of agglutinating properties. A still further advance was made in 1915 with the discovery that sodium citrate would prevent coagulation during transfusion, so that blood could be pooled and stored before use. Finally, the discovery of the Rh factor made it possible to give safely, after appropriate tests, the type of material that is desired. It is the treatment of choice after hemorrhage or loss from other causes, since it restores the volume and supplies all of the necessary proteins for normal metabolism. It is valuable in the treatment of shock, although plasma is equally so if there is no anemia. It is also used in various anemias, bacterial infections, uremias and blood poisoning of different kinds.

For these purposes, the blood is withdrawn from the donor into vessels holding enough sodium citrate to make 0.25 per cent, and the product can be stored for several weeks under appropriate conditions. However, the prothrombin and other compounds may gradually be lost, and it is better under some circumstances to use freshly drawn blood. Allergic reactions that sometimes develop include edema, bronchial asthma and skin rashes. Incompatibilities in unmatched blood will vary with the types, but the symptoms usually include chills, nausea, vomiting, fever and pain in the region of the kidneys.

Hemoglobin is available commercially as brownish-red scales that are soluble in water. It has been used as a treatment for various anemias in doses of 0.2 to 0.5 gram, but the amount of iron is very small and probably no more assimilable than inorganic forms, and intravenous injection is liable to produce reactions. The dried and powdered erythrocytes have been recommended for local application to wounds to stimulate healing. A preparation of globin from the erythro-

cytes has also been employed to promote diuresis in kidney diseases.

Citrated Normal Human Plasma (Normal Human Plasma) U.S.P.

is the sterile plasma obtained by pooling approximately equal amounts of the liquid portion of citrated whole blood from eight or more humans who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood transfusion at the time of drawing the blood. Each bleeding is drawn under aseptic precautions into individual sterile centrifuge bottles already containing 50 cc. of a sterile, 4 per cent solution of sodium citrate in isotonic sodium chloride solution for each 500 cc. of whole blood. The cell-free plasma is separated by centrifugation, and transferred to a pool by means of a closed system.

It must comply with the requirements of the National Institute of Health, and it may be stored as such, frozen or dried. The liquid plasma, which contains 5 per cent of dextrose to stabilize it, is a faintly yellow or amber liquid with a slight opalescence and no odor, in the absence of an odorous preservative. Frozen plasma, made by freezing quickly within 72 hours after bleeding and adding 5 per cent of dextrose, must be kept in this condition until liquefied for use by placing in a water bath at 37° C. Dried plasma, made by freezing the whole plasma without dextrose and drying in a vacuum until it contains not more than 1 per cent of moisture (lyophilization), has a light yellow to deep cream color, is microscopically of a honey-comblike structure and shows no evidence of fusion. It can be restored to the original volume by dissolving in 0.1 per cent citric acid in water for injection. The outside label for any of these products must bear the name; the volume of the original plasma; the manufacturer's lot number, name, address and license number; and the expiration date. The liquid and dried products are preserved at 15 to 30° C., the frozen products at not over -15 C°.

Plasma is used under the same conditions as whole blood but is preferred in most cases, except where the corpuscles are needed, such as in anemia. It has the advantages that it can be preserved more easily, that it can be administered in more concentrated form,

that it is less liable to give reactions and that in the desiccated form it can be transported more readily.

During World War II, a practical method of fractionating the plasma was developed by Cohn and associates.³ This consists of precipitation from hydro-alcoholic solution at low temperature and definite pH, both carefully controlled. The albumin, representing almost 60 per cent of the proteins, is obtained as a dry, white powder that is easily soluble in water. The 25 per cent solution, which has the same viscosity as plasma and can be used for the same purposes in one-fourth of the amount, has the advantages of convenience in storing and relative freedom from reactions. The gamma-globulin fraction contains most of the antibodies and promises to be of great value in the treatment of measles and other diseases whose antibodies are normally present in whole blood. The isoagglutin fraction has been found useful in the typing of blood before transfusion. The separated fibrinogen can be converted by thrombin, which is isolated in large quantities as prothrombin, into fibrin foam, a dry, white, brittle substance that is used as a surgical sponge. It has the advantage that it can be left in place and is ultimately absorbed without untoward reactions. The fibrinogen can also be recovered in the form of a thin sheet whose properties can be varied in such a manner as to make it useful in surgery in many ways. The isolated thrombin is available as a sterile powder to be used as such to stop bleeding or in the form of fibrin foam. The dried and powdered erythrocytes, obtained as a product in separating the plasma, have been employed as an application to wounds to stimulate healing, and the globin that can be released from them has been found useful in promoting diuresis in certain kidney diseases.

Normal Human Serum U.S.P. is the sterile serum obtained from eight or more humans under about the same conditions as for citrated plasma, except that the blood is allowed to coagulate for at least 12 hours, but

not more than 24 hours, before centrifugation, and that the citrate is omitted. Each lot of serum shall be aged in the liquid state for at least 28 days at 2 to 10° C., subsequent to the removal of the clot and prior to its use as liquid serum or prior to freezing and drying. The liquid is a slightly opalescent, faintly yellow or amber, practically odorless liquid, but may have the odor of any preservative and may become more opalescent or deposit some granules on standing. It is preserved at 2 to 10° C. The serum, when dried by lyophilization, has about the same properties as does dried plasma, and both products require similar labelling.

All three preparations are sometimes employed to replace blood, just as is the whole blood or plasma, but chiefly to provide antibodies in bacterial infections, especially measles. The antibodies that may be present in whole blood are concentrated in the serum, and in the serum from pooled blood it is almost certain that such as seem to persist for life will be present, particularly those for measles.

Human Measles Immune Serum (Measles Convalescent Serum) N.F. is a sterile serum obtained from the blood of a healthy human who has survived an attack of measles. It is collected under the same conditions as normal human serum and is subject to the same regulations by the National Institute of Health. It is a specific in measles, but it is not curative and can only ameliorate the symptoms and prevent the liability to bronchial pneumonia, mastoiditis, cardiac injury, etc. The official dose is 10 cc. in adults for prophylaxis or 4 to 8 cc. for infants, 20 cc. for therapy, all given intramuscularly.

Human Scarlet Fever Immune Serum (Scarlet Fever Convalescent Serum) N.F. is derived similarly from convalescents. It is subject to the same regulations and is recommended in identical doses.

Pertussis Immune Serum (Human) N.N.R. is a sterile serum prepared from the pooled blood of healthy adult human beings

who have had whooping cough and who have received repeated courses of Phase I Pertussis Vaccine. The blood is withdrawn about one month after the last course of vaccine, when the donor's serum has an agglutination titer of 1:2,560 or higher. The pooled serum is prepared, packaged and preserved according to the regulations of the National Institute of Health. It is used for the prophylaxis of whooping cough in a parenteral dose of 20 cc., which may be repeated at from 3 to 5 day intervals, or for treatment by three 20 cc. doses at intervals of 48 hours. Children who are critically ill may receive 60 to 100 cc. intravenously, and this dose may be repeated if necessary.

Human Immune Globulin U.S.P. is a sterile solution of antibodies obtained from the placental blood and the placentae expelled by healthy women, using a pool from at least ten individuals. The raw material is ground finely and extracted with a saline solution, and after filtration, the globulin fraction is precipitated by ammonium sulfate at a pH of 6.8. The precipitate is freed of salt by dialysis and dissolved in 1 per cent salt solution containing a preservative; the solution then is sterilized by filtration and is preserved at 2 to 10° C.

The product is used in the treatment of measles in order to modify the symptoms and complications, and although not entirely desirable, to prevent the disease in epidemics. It has the advantage over convalescent serum in that it is universally available, but it is prone to give undesirable reactions and is being supplanted by the gamma-globulin fraction of plasma. The doses to be used are governed by several factors that must be considered by the physician. Those doses recommended officially, 2 to 5 cc. for modification and 2 to 10 cc. for prevention, are given only as guides.

Brain Lipoid (Impure Cephalin, Impure Kephalin) N.N.R. is an extract of the brain of the ox or other mammals, prepared according to the method of Howell as applied in practice by Hirschfelder, and presumably

containing thromboplastic substances. It is used topically to prevent bleeding and has been recommended also for internal use for the same purpose, where it is probably of little value.

Solution of Brain Extract (Solution of Thrombin) N.N.R. is a similar product prepared by the method of Hess; it is used as is brain lipid.

Thrombin, Topical (Thrombin) N.N.R., a preparation of thrombin from bovine plasma after coagulation, is a white powder that is soluble in water or saline. It is intended as a topically applied hemostatic to control capillary bleeding in operative procedures; the dry powder or a solution in normal saline containing 1,000-2,000 units is used.

Antitoxic Serums are prepared by immunizing animals against the toxins of bacteria and, after bleeding, separating the globulin fraction. While any healthy animal can be used, the horse is generally selected for a variety of reasons, chiefly because it can furnish a large amount of blood and is particularly free from disease. The animals are given increasing doses every day by subcutaneous or intravenous injection until the antibodies have been built up enough to yield 500 units per cc. While continuing the injections, blood is removed at intervals until the animal fails to yield a product of the minimal standard or other conditions are unfavorable, usually after the production of from 22 to 30 liters. The serum is freed of fibrinogen and corpuscles, and the globulin fraction is separated by precipitation with ammonium sulfate and is further purified by precipitation at the isoelectric point. The collected precipitate is dissolved in 1 per cent sodium chloride containing a preservative, and the solution then is sterilized by filtering and packaged.

By Federal law, these products are placed under control of the National Institute of Health of the U. S. Public Health Service. The package must be marked with the name and address of the manufacturer, license

number, potency in antitoxin units and the expiration date, which is one year for those products that have 20 per cent more than the potency specified, two years for 30 per cent excess, three years for a 40 per cent excess and four years for 50 per cent excess. It must be preserved at 2 to 10° C., preferably at the lower limit, and must be dispensed in the original, unopened container of the manufacturer.

Reactions to injections of serum were formerly quite common and, while with modern highly purified serums the incidence has decreased, they still occur at the rate of about one to every 20,000 injections. The most common are in the nature of so-called serum sickness, which occurs about 5 to 10 days after injection and gives fever, urticaria and joint pains lasting for several days, but is not necessarily serious. Those who have previously received injections of the foreign serum may, in a much shorter time, get more intense symptoms of the same kind. Occasionally, patients may experience a severe and even fatal reaction (anaphylaxis) immediately after injection, causing flushing, dyspnea, cyanosis and other evidences of profound shock, and death may take place in a very few minutes. In every case of proposed injection of serums, the patient should be thoroughly questioned about previous similar treatment. In any event, sensitivity should be determined by an intradermal test with normal horse serum, which will give a wheal in a half hour, or by instillation of one drop of a 1:10 dilution of the serum into the conjunctival sac, where redness, swelling and itching will be produced in 15 minutes. When there is sensitivity to horse serum, a serum made from cattle blood may be used if available. The reactions can largely be avoided also by purifying the serum through selective digestion of the protein. This is preferably done by pepsin, or less commonly by trypsin or papain, and it does not interfere with the potency if performed properly.

Antibacterial Serums are made in a manner similar to that for antitoxic serums, but

attenuated bacteria are used as antigens. They are subject to the same regulations and can be expected to produce similar untoward reactions, because these are due to the foreign serum and not to the antigen or antibodies.

of an otherwise healthy animal suffering from rabies infection. The method of producing the material is to pass the virus from the medulla of a natural case in animals through about 30 to 40 rabbits until the normal incubation period of from 14 to 90

TABLE 59. COMMONLY USED SERUMS

SERUM	DOSES
Diphtheria Antitoxin U.S.P.	Therapeutic, 20,000 units; prophylactic, 1,000 units
Bivalent Gas Gangrene Antitoxin U.S.P.	One package or more
Trivalent Gas Gangrene Antitoxin U.S.P.	One package or more
Pentavalent Gas Gangrene Antitoxin U.S.P.	One package or more
Scarlet Fever Streptococcus Antitoxin U.S.P.	Therapeutic, 6,000 units; prophylactic, 2,000 units
Tetanus Antitoxin U.S.P.	Therapeutic, 20,000 units; prophylactic, 1,500 units
Tetanus and Gas Gangrene Antitoxins U.S.P.	One package or more
Staphylococcus Antitoxin N.N.R.	10,000 to 100,000 units
Botulinus Antitoxin N.N.R.	Therapeutic, 10,000 units; prophylactic, 2,500 units
Antivenin (<i>Latrodectus Mactans</i>) N.N.R.	2.5 cc.
Antivenin <i>Crotalus</i> N.N.R.	50 cc. or more
Tetanus Antitoxin, Bovine N.N.R.	As for Tetanus Antitoxin U.S.P.
Antimeningococcic Serum N.F.	20 cc.
Antipneumococcic Serum-Type Specific N.F.	20,000 to 100,000 units
Antidysenteric Serum N.N.R.	20 to 100 cc.
Antierysipeloid Serum N.N.R.	10 to 20 cc.

Vaccines are preparations of antigens, usually attenuated by some means, and administered in order to confer active immunity; the antibodies are developed in the patients' own blood. They are made from toxins or from bacteria.

Smallpox Vaccine U.S.P. is a glycerinated suspension of the vesicles of vaccinia (cowpox) which have been obtained from healthy vaccinated animals of the bovine family. The vesicles are removed under aseptic conditions at the time of suitable development, thoroughly triturated and made into a suspension with a watery solution or glycerin. The solution must be neither acid to bromocresol purple nor alkaline to phenol red. One female calf will furnish about enough material for 8,000 doses, and a single dose is enough to immunize a susceptible person, although the amount of protection gradually tapers off during ten years.

Rabies Vaccine U.S.P. is an uncontaminated suspension of the attenuated, diluted, dried or dead, fixed virus of rabies obtained from tissue of the central nervous system

days has been shortened to from 7 to 8 days. Several methods of attenuating this virus without increasing the period are employed, but the final result is to produce a material which will cause a mild form of the disease and build up an immunity. It is administered subcutaneously every day in the abdominal region for from 2 to 3 weeks, or in emergency, twice a day. The indications for its use are that the patient be bitten by a rabid animal and immediate isolation of the so-called negri bodies in the central nervous system of the killed animal. After such diagnosis, there is time to produce a mild form of the disease and protect the patient from the possible death that follows without treatment.

Diagnostic Diphtheria Toxin (Diphtheria Toxin For Schick Test) U.S.P. is a sterile solution of the toxic products of the diphtheria bacillus, containing in 5 cc. a minimum lethal dose for a 250 to 380 gram guinea pig in 96 hours. The solution contains substances to stabilize it, including buffer salts, peptone and human serum al-

bumin. The toxin is a protein that is fairly easily destroyed by heat, reagents, light, etc., but can be preserved for at least six months under right conditions, including temperatures below 10° C. The solution is given intracutaneously (arm) in a dose of 0.1 cc. (one-fiftieth of the minimum lethal dose) to determine if the patient has enough antibodies, a susceptibility being indicated by a circumscribed area of redness and swelling at the site of injection which remains for from 7 to 10 days. A control injection of inactivated toxin usually is made on the other arm.

Diphtheria Toxin-Antitoxin Mixture N.N.R. was formerly used to produce prophylactic immunity, but largely has been replaced by toxoid.

Diphtheria Toxoid (Diphtheria Antitoxin) U.S.P. is a sterile solution of the products of growth of the diphtheria bacillus so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity. The toxicity must be so low that five times the human dose does not cause either local or general symptoms in a guinea pig within 30 days. The antigenic value must be such that the initial dose for the human shall protect 80 per cent of guinea pigs, six weeks after injection, against five minimum lethal doses of the diagnostic test toxin. The product is preserved at 2 to 10° C., preferably at the lower limit, and by the addition of mercurials.

Attenuation of the toxin is possible because various reagents decrease the toxicity without interfering with its ability to induce production of antibodies. This process is usually affected by formaldehyde treatment. The dose for active immunization is 0.5 cc. or 1.0 cc., whichever is designated on the label, injected hypodermically and repeated twice at intervals of approximately 3 weeks. The immunity lasts for as long as five years.

Alum Precipitated Diphtheria Toxoid U.S.P. is made from the toxoid by precipitating it with alum and dissolving in isotonic

sodium chloride. The product is more effective than plain toxoid and is used in two doses about three weeks apart. It is apparently the best available agent for giving immunity from the disease, but it also is likely to give local abscesses which take a long time to clear up.

Tetanus Toxoid U.S.P. is a sterile solution of the products of growth of the tetanus bacillus, modified by special treatment to have less toxicity but retaining the property of inducing active immunity. The toxicity is so low that 5 cc. doses do not cause any symptoms of tetanus in guinea pigs within a period of 21 days. Antigenicity of the toxoid is such that a 1.0 cc. injection given to guinea pigs six weeks prior to an injection of ten minimum lethal doses of tetanus toxin will protect 80 per cent of them from all symptoms of tetanus for a period of 10 days. The dose used is 0.5 or 1.0 cc., whichever is specified on the label, repeated twice at intervals of about three weeks. The immunity begins to decrease after a few months but can be renewed by a single "booster dose."

Alum Precipitated Tetanus Toxoid U.S.P. is made from the toxoid in a manner similar to that used for the analogous product for diphtheria. It is administered in two 0.5 or 1.0 cc. doses 4 to 6 weeks apart.

Diphtheria and Tetanus Toxoids U.S.P. and Diphtheria and Tetanus Toxoids, Alum Precipitated U.S.P. are mixtures of therapeutically equivalent doses and are designed for children in that period of life when they are most liable to become infected with tetanus.

Scarlet Fever Streptococcus Toxin (Dick Test Toxin) U.S.P. is a sterile solution, in a medium containing not more than 1 per cent of peptone but no meat extractive, of certain products including a soluble toxin, resulting from the growth in the broth of suitable strains of hemolytic streptococci. The product is diluted 10 times before intracutaneous injection for diagnostic purposes, giving within 24 hours an area of redness at least 1 centimeter in diameter.

It may also be used for immunization, where it is injected subcutaneously or intramuscularly in increasing doses at weekly intervals until a negative Dick test is obtained. The initial amount is 500 to 650 skin test doses, or less if deemed advisable, the second 2,000 to 2,500, the third 8,000 to 10,000, the fourth 25,000 to 30,000, the fifth 80,000 to 120,000, each injection being 1 cc. The resultant immunity generally lasts ten to twelve years, but it is never absolute because several organisms may be involved in scarlet fever. Furthermore, agents such as penicillin and sulfa drugs are adequate for treatment, so that the immunological series are being used less often. One of the chief objections to the method, besides the fact that the immunity is not very satisfactory, rests in the more or less severe reactions that occur in about half of the cases. Attempts have been made to prepare a toxoid as with other toxins, but these have as yet been unsuccessful.

Scarlet Fever Streptococcus Toxin, Tannic Acid Precipitated N.N.R. is a suspension of the precipitated toxin containing 0.4 per cent of phenol as a preservative. It is claimed to permit slower absorption and give greater production of antibodies.

Staphylococcus Toxoid N.N.R. is a preparation of univalent or polyvalent toxins of *Staph. aureus* and *Staph. albus*, altered by the formaldehyde process. It is administered subcutaneously in the prophylaxis and treatment of localized infections caused by dermonecrotic and hemolytic toxins, as in carbuncles, boils and acne.

Typhoid Vaccine U.S.P. is a sterile suspension in isotonic sodium chloride solution or other suitable diluent of killed typhoid bacilli of a strain selected for high antigenic efficiency; it contains at least one billion organisms per cc. Selection of the strain is very important since there are at least three types of antigens; the killing agent is usually phenol or formaldehyde. The material is used almost entirely to protect against typhoid fever and is eminently successful

for this purpose. It is administered hypodermically in three graded doses of 0.5, 1.0 and 1.0 cc. at intervals of about a week. The injection almost always is followed by a local redness and pain, and there may also be headache and malaise, the more severe reactions usually being found in adults.

Typhoid and Paratyphoid Vaccine U.S.P. is a similar preparation, but also contains killed organisms (at least 250 million each) of the A and B bacilli of paratyphoid fever. It is used in the same doses and under the same conditions.

Epidemic Typhus Vaccine U.S.P. is a sterile suspension of the killed rickettsial organism of a strain or strains selected for antigenic efficiency and cultured in the yolk sac membrane of the developing (6 to 7 days) embryo of the chick. It is administered in three one cc. doses at from 7 to 10 day intervals, and a booster dose is given every six months when real danger of infection prevails.

Cholera Vaccine U.S.P. is a similar preparation from killed cholera vibrios and contains at least 8 billion organisms per cc. It is injected in three doses of 0.5, 1.0 and 1.0 cc. at from 7 to 10 day intervals, with a booster dose each year in cholera regions. With modern methods of selecting strains, the efficiency in preventing epidemics has increased considerably.

Plague Vaccine U.S.P. is prepared in a manner similar to that used for typhoid vaccine and contains in each cc. at least 2 billion killed plague bacilli that have been selected for high antigenic efficiency. It is used to prevent plague under the same conditions and in the same doses as cholera vaccine.

Staphylococcus Vaccine N.N.R. is prepared from cultures of *Staph. aureus*, *Staph. albus*, *Staph. citreus* or all three. An autogenous preparation from the patient is preferable, but a stock one from these organisms may be just as successful. The amount of material containing 1 to 1,000 million organisms is employed in carbuncles, boils and acne. A mixture of this with the toxoid has

been recommended for subcutaneous use at weekly intervals.

Pertussis Vaccine (Whooping Cough Vaccine) N.N.R. is a sterile suspension of the killed pertussis bacillus, consisting of carefully selected strains showing the characteristics of Phase I. The total dose, which has not been well-established, should be 15 to 45 billion organisms. It does not cure whooping cough, but it reduces the severity and especially the mortality from the disease. A topagen is also available for application to the nostrils.

Pertussis Vaccine, Alum Precipitated N.N.R. is claimed to be more effective, the total dose being 30 billion or more.

Pertussis Vaccine and Antitoxin Combined (Pertussis Endotoxoid-Vaccine) N.N.R. is recommended for producing active immunity but not for treatment.

Pertussis Vaccine Combined with Diphtheria Toxoid N.N.R. is recommended for producing active immunity against both diseases, using three injections of 1.0 cc. each at 3 to 4 week intervals.

Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids N.N.R. is administered in the same doses.

Yellow Fever Vaccine U.S.P. consists of a living culture of an attenuated strain of yellow fever virus selected for high antigenic activity and safety; it is made by culturing the virus in the living embryo of the chick. After processing, the culture is dried in the final containers from the frozen state, and the container is filled with nitrogen, sealed and preserved at a temperature not over 5° C. The product is required to have a potency such that each cc. contains at least 66,000 lethal doses when the vaccine is injected into mice intracerebrally. It is used for giving active immunity in a single subcutaneous injection of 0.5 cc.

Brucella Vaccine (Undulant Fever Vaccine) N.N.R. is a preparation of killed organisms of several species of *Brucella*, the causative organism of undulant fever. Its status as an effective therapeutic agent is

uncertain. It is injected subcutaneously or intramuscularly in an initial dose containing from 2 to 6 billion organisms, with subsequently increased doses at 2 to 5 day intervals until a total dose of 20 billion organisms is reached.

Old Tuberculin (Tuberculin-Koch, Concentrated Tuberculin, Crude Tuberculin) U.S.P. is a sterile solution in a special liquid culture medium of the soluble products of growth of the tubercle bacillus and should contain 50 per cent of glycerin. It is used chiefly for diagnostic purposes in man and other animals, usually in the Mantoux (intracutaneous) test or a modification, employing 0.1 cc. containing 0.01 cubic millimeter of the preparation. If no reaction is obtained in 48 hours, a 0.1 cubic millimeter dose in the same volume is injected, and a third dose of 1.0 cubic millimeter follows if this is negative. The positive reaction is a zone of redness and the presence of edema, usually with a papule at the point of injection, reaching a maximum in about 48 hours. This does not necessarily indicate a case of active tuberculosis, but a negative response almost completely excludes the disease. Old tuberculin sometimes is used to influence the progress of the disease, but the method is considered too dangerous for any one not experienced and is of questionable value in any event.

New Tuberculin N.N.R. is the name of several preparations that are practically bacterial vaccines. They are used in the same manner as Old Tuberculin.

B.C.G. Vaccine (Bacill Calmette Guérin), developed in Europe years ago in an attempt to immunize all infants against tuberculosis, is a culture of living bovine bacilli which have been attenuated. The death of 72 infants from tuberculosis at Lübeck (Germany) in 1931 was first attributed to the BCG strain used in their vaccination. Investigations revealed that a laboratory worker had contaminated the BCG strain with a normal virulent strain of the tubercle bacillus.

Recent investigations agree that the vaccine when properly prepared and used is harmless⁴ and will reduce the incidence of tuberculosis by more than 75 per cent.⁵ In recent years, the preparation has been introduced into this country with some reluctance, in spite of the presumably successful results in Europe.

Purified Protein Derivatives of Tuberculin U.S.P. (P.P.D.) is a sterile, soluble product of the growth of tubercle bacilli, prepared in a special liquid medium free from protein. This is being increasingly used to assist or replace tuberculin in diagnostic tests. It has the advantages of being very stable and of causing fewer reactions.

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30

Botanical Oleoresins, Resins and Balsams

OLEORESINS RESINS

OLEORESINS

Oleoresins are mixtures of oils and resins. Those of importance in pharmacy and medicine are obtained either by incising plant tissues or by subjecting dried portions of plant organs to alcohol, ether, acetone, or similar solvent extraction. These substances are generally insoluble in water or in dilute alcohol. Their oil portions often contain terpenes and oxygenated terpenes; whereas their resinous portions are made up of various phenolic resins, acids and esters.

As pharmaceutical preparations, oleoresins are often more potent than the fluid-extract of the same drug because they contain no solvent. But their constituents and action are not uniform. Usually oleoresins are employed in the form of an inunctuous mass or a thick liquid.

Turpentine (Gum Thus) N.F. Turpentine is the concrete oleoresin obtained from *Pinus palustris* Miller, (Fam. *Pinaceae*). Official Turpentine is a sticky yellowish-orange to pale yellow, irregular mass, becoming brittle in the cold. It possesses a characteristic odor. Chemically, the mass is composed of resin with approximately one-third volatile oil. It is soluble in alcohol, ether, glacial acetic acid and chloroform and

BALSAMS

is miscible with most fixed oils. When subjected to steam distillation, the oleoresin yields a volatile oil commonly known as "Spirits of Turpentine" (Turpentine Oil N.F.). The solid residue that remains is known as rosin (Rosin N.F.). Small amounts of dipentene, bornyl acetate, terpinolene and miscellaneous alkyl esters, ethers, phenols and phenolic hydroxy compounds are present in the oleoresin. A camphoric aldehyde which forms as an oxidation product in the oleoresin to some extent accounts for the characteristic turpentine odor. This odor can be removed or is rendered less intense following a washing process with the use of sodium hydroxide or in an atmosphere of carbon dioxide or by shaking with a solution of sodium bisulfite. For the constituents of Rosin, see under Resins.

The chief use of turpentine is as a source for official Turpentine Oil and Rosin. However, the concrete oleoresin occasionally finds use as a stiffening agent for ointments and cerates. Its volatile oil fraction is generally employed for local irritation effects and solvent properties. (See Turpentine Oil.) The solid rosin fraction enters into some plasters and ointments (see Rosin).

OFFICIAL OCCURRENCE N.F.	PER CENT TURPENTINE
Compound Rosin Cerate	12.0

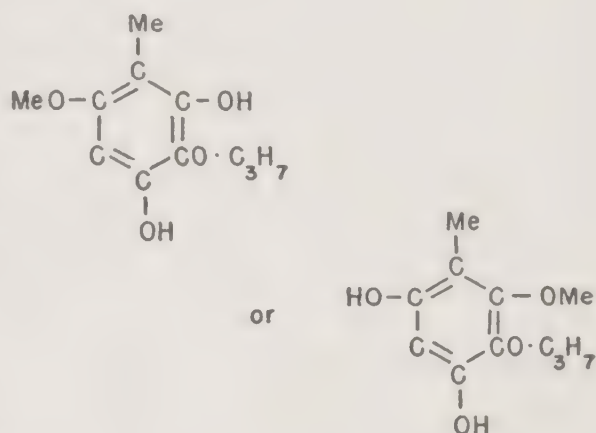
Allied Turpentes. Most conifers, such as pines, balsams and larches, yield an exudate upon injury or even spontaneously. There are, therefore, many turpentes of unofficial status. Some of these differ from the turpentine of *Pinus palustris* in that their oils contain carenes and are known as carene type oils. According to Simonsen,¹ carene type oils oxidize more rapidly than do the pinene type oils. Among allied turpentes are Venice turpentine and Canada turpentine. The latter is commonly known as Canada balsam. Both of these products are used as mounting media in histologic technics.

Aspidium Oleoresin (Male Fern Oleoresin) U.S.P. Aspidium Oleoresin is an ether extract obtained from the rhizomes and stipes of the European Aspidium or of American Aspidium. "It yields not less than 24 per cent of crude filicin." The official Oleoresin of Male Fern is a viscid to semiviscid, dark-green liquid with a bitter taste and characteristic fernlike odor. Heavier, dark, granular deposits often separate from the oleoresin during storage. These should be mixed thoroughly with the liquid portion before it is used.

The constituents of Aspidium Oleoresin have been variously described^{2, 3} and named filmarone, crude filicin, filicic acid, aspidinol, aspidin, albaspidin, flavaspidic acid, etc. Pabst and Bliss² state that the active constituent is crude filicic acid. It has been shown by others⁴ that the taenicide activity of the drug is caused by several of its constituents in combination rather than by any single one and that the extract from dried crude drug material is as effective as that from fresh material.

Robertson and Sandroek,³ through synthesis, found that aspidinol is a phloroglucinol derivative. They establish further evidence that it is a monomethyl ether of C-

methylphloro-*n*-butyro-phenone with the following structure:



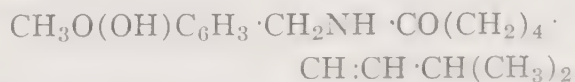
The oleoresin is used principally as a taenifuge because it renders the tapeworm totally paralyzed so that the scolex (head) releases its grasp and the worm can be washed out with a purge. However, it is generally not effective when so used for other helminthes. Care should be exercised in the selection of a proper intestinal lavage which is to be used with Aspidium therapy. Fasting and the use of a saline cathartic or enema should precede the administration of the oleoresin. Seven to ten day intervals should be observed before repeating the therapy.

The oleoresin is administered in capsular form or in a palatable vehicle.

The average dose is 4 Gm.

Capsicum Oleoresin N.F. The oleoresin of *Capsicum* is prepared by extraction of powdered Capsicum N.F. with acetone or ether. It is a dark, pungent, reddish-brown, viscid liquid with a slight odor of the fruit. The oleoresin should be devoid of fatty residual.

The most important constituent of the oleoresin of capsicum is a vanillylamide of isodecenoic acid, named capsaicin and declared by E. K. Nelson⁵ to have the following structure:



This is a white, crystalline substance which is almost insoluble in water, but dissolves

freely in alcohol, ether and alkalies. Capsaicin is prepared by macerating the oleoresin with mineral oil; this is followed by extraction with alcohol and subsequent purification. It should be stored in airtight containers.

Capsicum, in the form of its oleoresin and tincture, is used generally for its stimulant and condiment action. Capsicum ointment and plasters, such as rubber capsicum plaster, resin plaster and diachylon plaster, have been employed as counterirritants. The irritant effects of the oleoresin upon sensory nerve endings differ from those of other such drugs in that they are accompanied by very little capillary dilatation. Hence, there is no appreciable redness or rubefacient action to the skin.

The average dose is 15 mg.

OFFICIAL OCCURRENCE N.F.	PER CENT OLEORESIN
Capsicum Ointment	5.0

Additional oleoresins of lesser importance are those of cubeb, copaiba, parsley and pepper. The sources and principal constituents of these are presented in Table 60 (see page 587).

RESINS

Naturally occurring resins are generally solid, amorphous or crystalline substances formed in plants in combination with oils, balsams, gums, glycosides and tannins. Frequently, resinous products bear the name of their combination with these substances such as the oleoresin, gum-resin, glycoside and tannol-resin. The so-called "gum-resins" and "oleo-gum-resins" contain true gums in their natural state. However, if the resin has been obtained by solvent extraction, true gums are no longer in combination with it.

Many resinous drugs are prepared in pillular form; others are dispensed as extracts, tinctures or emulsions. Occasionally the powdered crude resin is used. Soluble preparations of resins and balsams such as

myrrh soluble, benzoin fluid, tolu soluble, etc. generally consist of hydro-alcoholic concentrates prepared from the natural product. Such fluids have been freed of granular or precipitated resins and made sufficiently concentrated so that the pharmacist can more conveniently prepare tinctures, syrups, ointments or other preparations from them.

Rosin (Colophony) N.F. Rosin is a solid resin obtained from species of pine. The official rosin is the residue separated from crude oleoresin of turpentine (see Turpentine Oleoresin N.F.) during the production of turpentine oil. Usually, such rosin is termed *gum rosin* because of its physical form, and is of a light yellow to "water white" color. Rosin also is obtained as a product of the extraction or distillation of pine wood. Such rosin is called *wood rosin* and is darker yellow in color than *gum rosin*. Much of this resin is composed of an unsaponifiable substance called *resene*, which accounts in part for its darker color.

Rosin liquefies at a temperature of between 130° and 150° C.; it is soluble in alcohol, ether, benzene, glacial acetic acid, trichloro- and tetrachloro-ethylenes, fixed and volatile oils. It contains a mixture of anhydrides and isomers of a diterpene carboxylic acid, abietic acid. Among these are primaric and sapinic acids. Methyl, ethyl and glyceryl esters of abietic acid are made use of in the manufacture of plastics, varnishes, synthetic resins and nitrocellulose coatings.

Rosin spirit is a light, oily liquid formed following the dry distillation of *Rosin* at high temperatures. *Rosin oil* is a fraction of the same distillate taken at a higher temperature.

Rosin is used as a vehicle in the preparation of cerates, soaps, collodions and plasters. Therapeutically, it probably exerts some stimulating and antiseptic properties. It also is employed extensively for industrial purposes.

TABLE 60. OLEORESINS

NAME	SOURCE	PRINCIPAL CONSTITUENTS	REMARKS
Cubeb Oleoresin	An alcoholic extract of dried unripe fruit of <i>Piper cubeba</i> (<i>Piperaceae</i>)	Mostly volatile oil with the sesquiterpene, Cadinene, and other terpenes. Resin portion with cubebic acid and phenolic resin, cubebin.	Deteriorates during exposure to air. Cubebic acid antiseptic; urinary antiseptic. Is official in <i>National Formulary</i> .
Copaiba Oleoresin	A natural exudation from South American species of <i>Copaifera</i> (<i>Leguminosae</i>)	Crystalline and amorphous resin acids, including copaivic acid; also volatile oil containing caryophyllene.	Useful in lacquer and varnish manufacture. Intensely irritating to genito-urinary tract. Is official in <i>National Formulary</i> .
Parsley Oleoresin (Oil of Parsley Seed)	An ether extract of the dried fruits of Parsley, <i>Petroselinum</i> spp. (<i>Umbelliferae</i>)	Contains the apiol components—crystalline apiol, apiolin and myristicin.	Crystalline apiol, (1-allyl-2,5-dimethoxy-5,4-methylene-dioxybenzene) and other constituents shown by Lutz ⁶ to produce marked fall in blood pressure and epileptiform convulsions. Stimulant.
Pepper Oleoresin	An ether extract of the dried unripe fruits of <i>Piper nigrum</i> (<i>Piperaceae</i>)	Alkaloids piperine, piperidine and chavicine. (See under Alkaloids.) Pungent effects are from chavicine. (See Ott and Ludemann. ⁷) In the volatile oil the principal terpene is <i>levophellandrene</i> .	The oleoresin also is obtained from root portions of the plant. Stimulant and condiment.

OFFICIAL OCCURRENCE	PER CENT ROSIN
N.F.	
Rosin Cerate	35.0
Compound Rosin Cerate....	23.0

Cannabis (Marihuana). Cannabis consists of the dried flowering tops of the female plants of *Cannabis sativa* L. It is a mixture of leaves, floral parts and resins. Often the recently cut flowering tops are referred to as *ganja*. Larger leaf and twig portions are bundled together and called *bhang*. The resin is separated from the leaf and twig material by mechanical kneading or expression. This is physiologically the most active portion of the plant and is called *charas* or *hashish*. Alcoholic and ethereal extracts of all portions of *Cannabis* have been used in medicine.

The substances cannabiniol and cannabidiol have been isolated from the reddish, oily, active fraction of the resin by vacuum distillation. The physiologic activity of cannabis is centered in an isomer of cannabidiol, tetrahydrocannabinol.^{8,9,10,11} It is probable that the highly active isomeric form of cannabidiol tetrahydrocannabinol, is a precursor of cannabiniol in the plant. The latter form is less active physiologically. Analogues of tetrahydrocannabinol have been made synthetically. One of these, a dibenzopyran (1-hydroxy-3-n-hexyl-1,6,6,9-trimethyl-7,8,9,10-tetrahydro-6 dibenzopyran) known as synhexyl has been used to produce euphoria and relaxation in thalamic dysfunction.¹² This is a viscid, pale-yellow and translucent resinous substance, insoluble in water, but soluble in organic solvents. Other constituents present in the resin include a volatile oil containing terpenes, sesquiterpenes and choline.

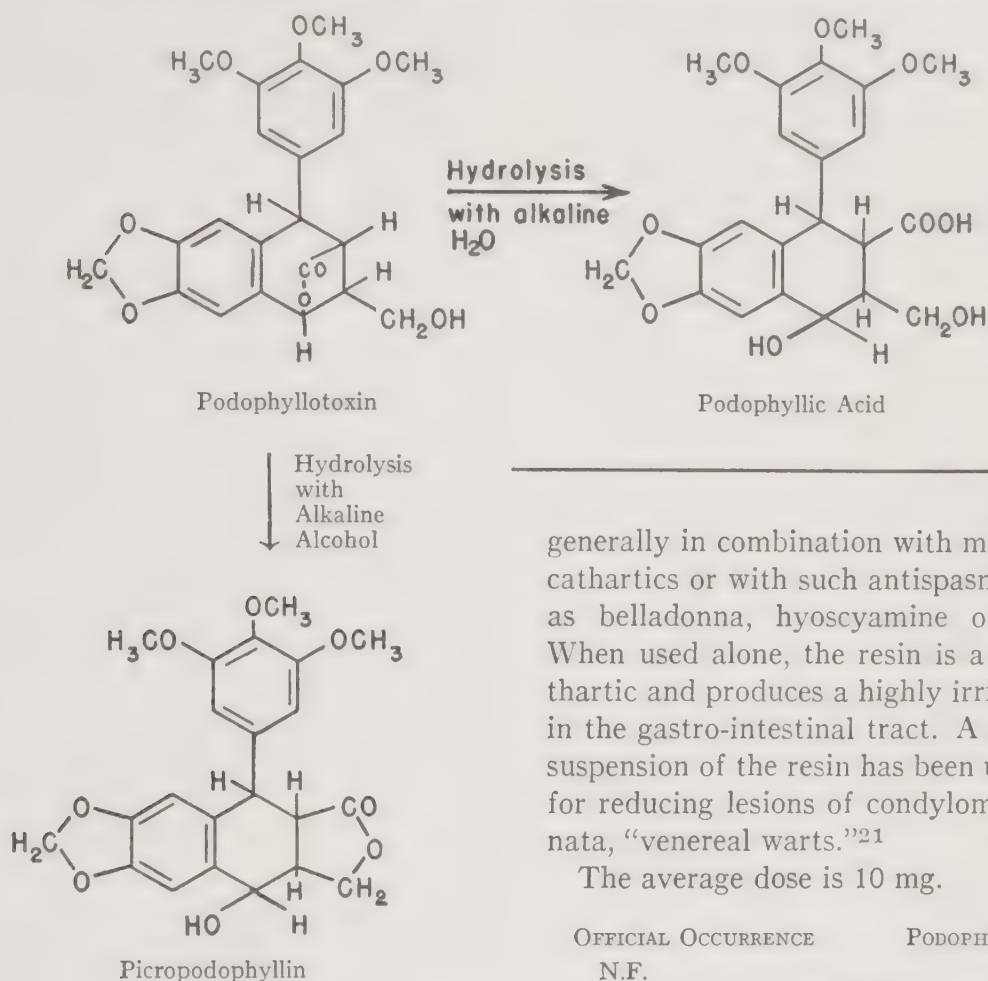
Cannabis has been used in medicine to produce narcosis and sedation. Its action is almost entirely on the central nervous system, where it exerts a combination of depression and stimulating activity characterized by vivid hallucinations and violent behaviorisms.

Podophyllum Resin (Podophyllin) N.F.

Podophyllum Resin N.F. is a mixture of resins obtained by alcoholic extraction from the dried rhizome and roots of the common May apple, *Podophyllum peltatum* L. It is insoluble in water and only slightly soluble in ether, chloroform or alcohol. It will dissolve to form a yellowish liquid in potassium or sodium hydroxide T.S.

Chemically, the chief active components isolated from the resin include an amorphous substance, podophylloresin, to which most of the cathartic action is due and crystalline fractions, podophyllotoxin, its isomer, micro-podophyllin, and podophyllic acid. These substances have been shown to possess varying degrees of physiologic action.¹³ Podophyllotoxin and podophyllic acid possess cathartic action to a lesser degree than the amorphous podophylloresin. Both have irritating and toxic effects on membranes, the former being more irritating. Recently, the anticarcinogenic activity of these substances has been re-investigated. Evidence has been shown by King and Sullivan,¹⁴ Sullivan,¹⁵ MacCardle,¹⁶ Cornman,¹⁷ Ormsbee and Cornman¹⁸ and others that podophyllin exerts a chemotherapeutic action within cell nuclear or chromosome phases resembling that of colchicine. These workers offer interesting data to show the carcinolytic-type action of the resin. Fundamentally the action delays or completely inactivates some mitotic cellular figures after the metaphase stage is reached. Such activity shows promise of repressive effects against some animal tumors. A schematic relationship of these tricyclic compounds is shown on page 589.

Viehoever and Mack¹³ have reviewed the chemistry of the resinous mixture. Podophyllotoxin is a white, crystalline substance occurring in anhydrous and hydrous forms. Crystals are insoluble in water and ether. Podophyllic acid has been isolated from the resin in amorphous and crystalline form. It is soluble in alcohol and chloroform, and practically insoluble in petroleum, ether or water. Crystals are colorless and prismatic and wider in diameter than those of podophylloresin.



generally in combination with milder acting cathartics or with such antispasmodic drugs as belladonna, hyoscyamine or atropine. When used alone, the resin is a drastic cathartic and produces a highly irritant action in the gastro-intestinal tract. A 25 per cent suspension of the resin has been used locally for reducing lesions of condylomata acuminata, "venereal warts."²¹

The average dose is 10 mg.

OFFICIAL OCCURRENCE PODOPHYLLUM RESIN N.F.

Aloin, Cascara, Belladonna and Podophyllum Pills .	1.0 Gm./100 pills
Compound Colocynth and Jalap Pills	1.5 Gm./100 pills

phyllotoxin. Picropodophyllin occurs in white needles and is freely soluble in alcohol, methanol or chloroform and insoluble in water. A white, crystalline compound recently isolated from podophyllin by the National Cancer Institute group¹⁹ and labelled N.C.I. No. 1074 or α -peltatin resembles this substance in several aspects. Both podophyllotoxin and picropodophyllin form oxalic acid when oxidized with nitric acid, and when fused with alkalis, they form orcinol and acetic acid.

The yellowish-brown color present in the resin is linked with the presence of a penta-hydroxyflavone, podophylloquercetin, probably formed by the hydrolysis of quercetin,²⁰ which is a yellowish glycoside present in the rhizome and roots of the plant.

Podophyllum resin is used as a cathartic

Jalap Resin N.F. Jalap Resin is a glycosidal resin obtained from the dried tuberous roots of *Exogonium purga* (Wonderoth) Bentham (Fam. *Convolvulaceae*). It is extracted from the dried, powdered, crude drug by percolation with 9 volumes of alcohol and 1 volume of water. Following concentration of the syrupy liquid, the resin is precipitated by means of hot water, then washed thoroughly and dried. It is insoluble in hot or cold water, fixed and volatile oils, benzene or carbon disulfide. It forms a brownish-yellow solution with alcohol, ether or chloroform and is slowly soluble in alkali solutions.

The glycosides, convolvulin and jalapin, have been isolated from the resin mixture.²² Additional substances include tiglic, exogonic, isovaleric and methylethylacetic acids.

Convolvulin is insoluble in ether but is soluble in alkali solutions. It is intensely irritating to membranes. Jalapin is soluble in ether and alkaline solutions. Upon hydrolysis, it yields jalapinol or convolvulinolic acid and dextrose. Valett²³ has shown evidence of antibiotic action from jalapin. Resin of jalap has been used as a drastic cathartic, but when so used, its action is intensely irritating. It usually is employed in combination with other mildly acting cathartics and antispasmodics.

The average dose is 0.125 Gm.

OFFICIAL OCCURRENCE	JALAP RESIN
N.F.	
Compound Colocynth and Jalap Pills	2 Gm./100 pills
Compound Mild Mercurous Chloride Pills	2 Gm./100 pills

Ipomoea Resin (Mexican Scammony Resin) N.F. Ipomoea Resin, often referred to as "Scammony Resin," is a glycosidal resinous mixture obtained from the dried roots of *Ipomoea orizabensis* Ledebour (Fam. *Convolvulaceae*).

Ipomoea Resin occurs in hard to brittle, yellowish-brown masses. It has a characteristic cheeselike odor said to be due to a volatile fatty acid developed during the drying process. The resin is soluble in alcohol, ether and chloroform, and only slightly soluble in petroleum benzin. It is slowly soluble in alkaline solutions, forming opaque solutions which do not gelatinize upon standing.

The resin is complex in composition. Among its constituents is an ether-soluble glycoside called scammonin, which is similar to jalapin of Jalap Resin. It is a white, amorphous substance which hydrolyses in alkali medium to form scammonic acid, scammonolic acid and glucose. Scammonin, in the presence of mineral acids, forms the anhydrides scammonol, valeric acid and sugars. The resin acids resemble the character of the glucosidal derivatives and esters of convolvulinolic acid present in jalap. Among additional constituents present in the resin are scopoletin, an alcohol-soluble

fraction, dihydroxycinnamic acid and volatile oil.

Ipomoea Resin is used as a drastic cathartic and frequently is combined with other milder acting cathartics and antispasmodic drugs.

The average dose is 0.2 Gm.

OFFICIAL OCCURRENCE	PER CENT IPOMOEA RESIN
N.F.	
Compound Colocynth Extract . .	14.0

Guaiac (Guaiac Resin) N.F. Guaiac Resin is obtained from the wood of *Guajacum officinale* L. or of *Guajacum sanctum* L. (Fam. *Zygophyllaceae*). "Guaiac yields not more than 15 per cent of alcohol insoluble residue."

Guaiac resin of commerce is in the form of large or small masses or small, rounded, tear-shaped lumps. The latter often represent spontaneous exudates from the wood. Its color is brownish-black to greenish-brown. A green color develops upon exposure to air.

It is insoluble in water, slightly soluble in benzene or carbon disulfide, but is freely soluble in alcohol, chloroform, ether or alkali solutions. The resin will form pharmaceutical incompatibilities with mineral acids, iron salts, gold chloride, permanganates or similar oxidizing agents. In dispensed mixtures it is convenient to suspend the resin with mucilage of acacia or another suspending medium.

The Ammoniated Guaiac Tincture N.F., which is made by using aromatic ammonia spirit as the menstruum, has been employed as an antirheumatic and diaphoretic. The presence of the ammonia partially saponifies the resin and reduces the amount of resin precipitation in the tincture. Occasional use is made of the resin as a clinical laboratory reagent for enzyme detection in blood, some plant extracts or cyanogenetic glycosides. It produces a blue color in the presence of oxidizing enzymes. Guaiac is of some value as an antioxidant in the preservation of lard. This preserving quality may be enhanced

considerably when the resin is combined with nordihydroguaiaretic acid.²⁴

The average dose is 1 Gm.

OFFICIAL OCCURRENCE	PER CENT GUAIAIC RESIN
N.F.	
Ammoniated Guaiac Tincture. . .	20.0

Mastic N.F. Mastic resin is a concrete resinous exudation obtained from the inner bark of *Pistacia lentiscus* L. (Fam. *Anacardiaceae*). It occurs in ovate to pear-shaped, yellow to greenish-yellow, smooth tears. "Mastic yields not more than 3 per cent of ether-insoluble residue, and not more than 20 per cent of alcohol-insoluble residue."

The constituents of mastic are not entirely understood. However, Tschirch²⁵ and Casparis and Naef²⁶ have shown it to be made up of a number of free resin acids and resenes (probably about 70 per cent). Among the amorphous resin acids are the masticinic acids and their isomers. The mastic resenes include masticoresene, an alcohol-soluble substance and its alcohol-insoluble isomer, masticoresene. The latter resene has a camphoraceous odor. Other constituents of the resin are a volatile oil (about 2.5 per cent) consisting chiefly of *d*-pinene and a water-soluble, bitter principle.

Mastic occasionally is combined with drastic cathartic resins to mitigate their action somewhat. In dentistry it has been found useful as a filling ingredient and it has been advocated as an enteric coating for pills.²⁷ Some use is made of it in varnishes.

OFFICIAL OCCURRENCE	MASTIC RESIN
N.F.	
Aloe and Mastic Pills.	4 Gm./100 pills

Since resins are formed in plant secretion sacs or reservoir ducts, some remain affixed to volatile oils and gums. Such resins are termed oleo-gum-resins or gum-resins. The drugs Asafetida, Myrrh and Gamboge are examples of this type of resinous plant product. In each case the gum portion is a water-soluble true gum.

Asafetida (Gum Asafetida) N.F. Asafetida consists of the oleo-gum-resin from the

incised living rhizomes and roots of several species of *Ferula* (Fam. *Umbelliferae*). "Asafetida yields not less than 50 per cent of alcohol-soluble extractive."

As this resin often occurs mixed with allied gums and resins, several qualitative tests and standards have been devised for such admixtures. These are largely color reactions produced by the addition of alkalies and acids to water and alcoholic extracts of the resin. Among such foreign resins are those of galbanum, ammoniac and rosin.*

Asafetida probably contains 60 to 70 per cent resin, about 30 per cent gum and the remainder volatile oil. The resinous portion, which is acetone-soluble, contains ferulic acid in combination with its ester, asaresinol. The latter is responsible for some of the color changes in the resin. Ferulic acid oxidizes to form vanillin. The volatile oil fraction consists of a sulfhydryl component, hexenyl sulfide, and a disulfide.²⁸ Much of the offensive odor is present in this oil.

Asafetida has essentially a mild irritant action on the mucous membranes of the gastro-intestinal tract. Because of this action, it has been used as a stimulant, carminative and laxative. It often is employed in enema form. The resin has an intensely offensive odor.

The average dose is 0.4 Gm.

OFFICIAL OCCURRENCE	PER CENT ASAFETIDA
N.F.	
Asafetida Pills	20 Gm./100 pills
Asafetida Tincture	20.0

Myrrh (Gum Myrrh) U.S.P. Myrrh is an oleo-gum-resin obtained from African and Arabian species of *Commiphora* (Fam. *Burseraceae*). "Myrrh yields not less than 30 per cent of alcohol-soluble extractive." The official oleo-gum-resin is a yellow to reddish-brown agglutinated mass of rounded to irregular tears, with a characteristic aromatic balsamic odor and bitter taste. It is partly soluble in water, alcohol or ether. It forms a yellow-white emulsion with water and a viscous liquid when mixed with alkalies. The

* See the National Formulary for particulars.

alcoholic tincture (Myrrh Tincture U.S.P.) should be clear and have no separated resin particles.

The chemical constituents isolated from the volatile oil of myrrh include cuminaldehyde, eugenol, limonene, a tricyclic sesquiterpene, heerabolene, dipentene, pinene, *m*-cresol and phenols. The gum portion contains much mucilage, comprised largely of arabin, which upon hydrolysis yields arabinose. The resin residue contains a mixture of resin acids, resenes and terpenes whose structures are not entirely understood. Accordingly to Friedrichs,²⁹ these include commiphoric acid, α -heerabomyrrhol, β -heerabomyrrhol, heeraboresene, α -myrrhoidic acid and β -myrrhoidic acid. Bitter principles and mineral elements are also present.

Gum Myrrh in the form of its official tincture is occasionally prescribed in medicine for its local action as a mild gastro-intestinal stimulant. It has also been used as a mouth wash ingredient for its stimulant and aromatic virtues.

OFFICIAL OCCURRENCE	PER CENT MYRRH
U.S.P.	
Myrrh Tincture	2.0

Gamboge N.F. Gamboge is an oleo-gum-resin ("Gum Resin" N.F.) obtained from *Garcinia Hanburyi* Hooker filius (Fam. *Guttiferae*). "Gamboge yields not less than 65 per cent of alcohol-soluble extractive." It occurs in cylindrical, dark-brown rolls or as broken, irregular, resinous masses called "cakes." The oleo-gum-resin is odorless and forms a yellow-brown emulsion with water. It is partially soluble in alcohol, but is soluble in alkali solutions and in strong mineral acids. Most of the resin portion is ether-soluble.

The chemical constituents of gamboge resin are rather obscure. It contains the resin acids α -, β - and γ -garcinolic acids. The gum fraction is water-soluble and yields sugars of the arabinose type upon hydrolysis.

Gamboge has been employed as a drastic cathartic. It is severely irritating, however, to the alimentary tract and is, therefore,

almost never administered alone. It has been used occasionally in veterinary medicine.

The average dose for adults is 0.125 Gm. and that for cattle is 1.5 Gm.

OFFICIAL OCCURRENCE

GAMBOGE

N.F.

Compound Mild Mercurous

Chloride Pills 2 Gm./100 pills

BALSAMS

Balsams are resinous mixtures which form in plants either as natural products of cell metabolism or as the result of injury to tissues. These resins usually contain variable quantities of volatile oils and esters of benzoic and cinnamic acids.

Benzoin U.S.P. (Gum Benjamin). Benzoin is a balsamic resin obtained from several species of the genus *Styrax* and its section, *Anthostyrax*. It is known commercially as Sumatra and Siam Benzoin. "Sumatra Benzoin yields not less than 75 per cent of alcohol-soluble extractive. Siam Benzoin yields not less than 90 per cent of alcohol-soluble extractive."

The official benzoin from Sumatra and Siam differ from each other in their physical form and content of cinnamic acid and benzoic acid. Sumatra Benzoin contains about 6 to 7 per cent free benzoic acid, whereas Siam Benzoin contains almost twice that amount (about 12 per cent). Upon boiling an acidulated solution of the Sumatra variety with an oxidizing agent, such as potassium permanganate, an odor of benzaldehyde evolves. This is made use of in the U.S.P. tests for cinnamic acid in the latter resin. Other constituents common to both varieties of Benzoin, but in varying amounts, include a crystalline benzoate, coniferyl benzoate, a triterpene acid, siarresinolic acid. (Siarresinal) in Siam Benzoin and sumaresinolic acid (Sumaresinol) in Sumatra Benzoin.³⁰ Additional acids and esters of cinnamic and benzoic acids are present. A portion of the fragrant odor is due to the presence of vanillin.

Benzoin is used as an ingredient in Benzoin Tincture and in Compound Tincture of

Benzoin. The latter is employed as a inhalant in the relief of respiratory congestions. The antiseptic and preservative virtues of benzoic acid in addition to other constituents of the balsam, notably coniferyl benzoate,³¹ are of value in its use as an external antiseptic and a preservative of fats and oils. It has been used as a fixative in some perfumes.

OFFICIAL OCCURRENCE	PER CENT BENZOIN
U.S.P.	
Compound Benzoin Tincture	10.0
Benzoin Tincture	20.0
Benzoinated Lard	1.0

Storax (Liquid Storax) U.S.P. Storax is a balsam obtained from the trunk of *Liquidambar orientalis* Miller or from *L. styraciflua* L. (Fam. *Hamamelidaceae*). The former species yields Levant storax; the latter species yields the commercial American storax.

The official Storax from either of the above sources is a more or less soft yellow-brown to amber-colored balsam, becoming darker in color and harder upon exposure to air. It is insoluble in water and miscible with ether, acetone, xylene and similar balsam solvents. Crystals of cinnamic acid and its esters occasionally separate out.

Among the more important constituents of this balsam is an amorphous alcohol resin, α - and β -storesin. This probably makes up of from 30 to 50 per cent of the balsam mixture. The esters, cinnamyl cinnamate (Styracin) and phenylpropylcinnamate, constitute about 18 per cent of the balsam. Varying amounts of styrene also are present.

The chief use of Storax pharmaceutically is in the preparation of Compound Benzoin Tincture. In this mixture it probably exerts some action as a stimulating expectorant. It has been used in parasiticide remedies and as a perfume in soaps.

OFFICIAL OCCURRENCE	PER CENT STORAX
U.S.P.	
Compound Benzoin Tincture	8.0

Peruvian Balsam (Peru Balsam) U.S.P. Peruvian Balsam is a dark brown liquid bal-

sam obtained from the trunk of *Myroxylon Pereirae* (Royle) Klotzsch (Fam. *Leguminosae*). It has a sweet, vanillalike odor and a bitter taste. The liquid is miscible with alcohol, chloroform, acid and glacial acetic acid. It is insoluble in water and slightly soluble in petroleum benzin and in ether. There is usually a slight milky opaqueness developed following the mixture of the balsam with petroleum benzin and ether.

The most important constituents of Peruvian Balsam are confined to its volatile oil fraction. Among these are esters of benzoic and cinnamic acids, such as *benzyl benzoate*, *benzyl cinnamate* and *cinnamyl cinnamate*. Vanillin and a tertiary alcohol, *nerolidol*, are probably responsible for the characteristic odor of the balsam. The oil is called cinnamein and is present to the extent of about 60 to 70 per cent.

In the resinous portion of the balsam there are present varying amounts of cinnamic acid and its esters together with resin alcohols, notably peruresinol.

Peruvian Balsam is used most commonly as a protective and parasiticide. As such it is often mixed with zinc oxide and castor oil in variable amounts. Incompatibilities are often formed when the balsam is mixed with sulfur and fats such as lard. A more homogeneous ointment can be made by first incorporating the balsamic resin in lanolin or castor oil. It has been applied in wound dressings and dental sockets as a protective.

OFFICIAL OCCURRENCE	PER CENT PERUVIAN BALSAM
N.F.	

Compound Acetylsalicylic Acid Paste	10.0
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Tolu Balsam (Tolu) U.S.P. Tolu Balsam, unlike Peruvian Balsam, is very resinous in character and might well be regarded as a balsamic resin. It is a solid to semisolid balsam obtained from incising the trunk and branches of *Myroxylon Balsamum* (Linné) Harms, (Fam. *Leguminosae*).

The official Tolu Balsam is a yellowish-brown to darker brown, viscid balsam which

becomes more solid and brittle upon aging. It has a characteristic, vanillalike, aromatic odor. The balsam is practically insoluble in water and petroleum benzin. It is soluble in alcohol, chloroform ether, volatile oils, and partially soluble in sodium and potassium hydroxide solutions.

The constituents of the balsam are similar to those of other balsams, but unlike Peruvian Balsam, Tolu Balsam contains chiefly resin components. There is approximately 70 to 80 per cent of a resinous complex in the balsam. In this are cinnamic and benzoic acids and esters. Other resin constituents are toluresino-tannol and vanillin. The volatile oil portion is very small, probably about 2 to 4 per cent, and contains benzyl benzoate and benzyl cinnamate in addition to other components.^{32,33}

Tolu Balsam is used in cough syrup mixtures as a stimulating expectorant. Other uses include its mildly antiseptic action as a parasiticide and its fixative properties in cosmetics and perfumes.

OFFICIAL OCCURRENCE	PER CENT TOLU BALSAM
U.S.P.	
Tolu Balsam Tincture.....	20.0
Compound Benzoin Tincture.....	4.0
Tolu Balsam Syrup (from the Tincture)	1.0

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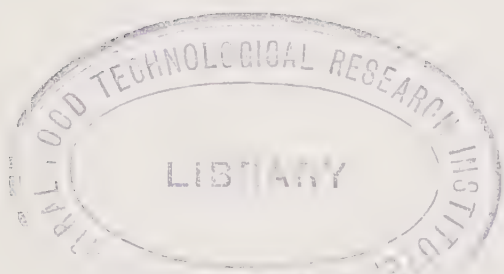
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